Robin Sequence:

Clinical implications

and functional outcomes following

(non-) surgical management

Pleun van der Plas

Colofon

Robin Sequence: Clinical implications and functional outcomes following (non-) surgical management

ISBN: 978-90-833330-3-8

The studies described in this academic dissertation were performed at the Craniofacial Research Unit of the Department of Oral- and Maxillofacial Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands.

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Cover design & illustrations: E.J.M.B. van Hattem

Printing: proefschriften.nl – *www.proefschriftenprinten.nl*

Robin Sequence:

Clinical implications and functional outcomes following (non-) surgical management

Robin Sequentie:

Klinische implicaties en functionele uitkomsten na (niet-) chirurgische behandeling

Proefschrift

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam

op gezag van de rector magnificus

Prof. dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op

vrijdag 30 juni 2023 om 10.30 uur

door

Pleunke Pietronella Johanna Maria van der Plas

geboren te Oosterhout (NB)

Erasmus University Rotterdam

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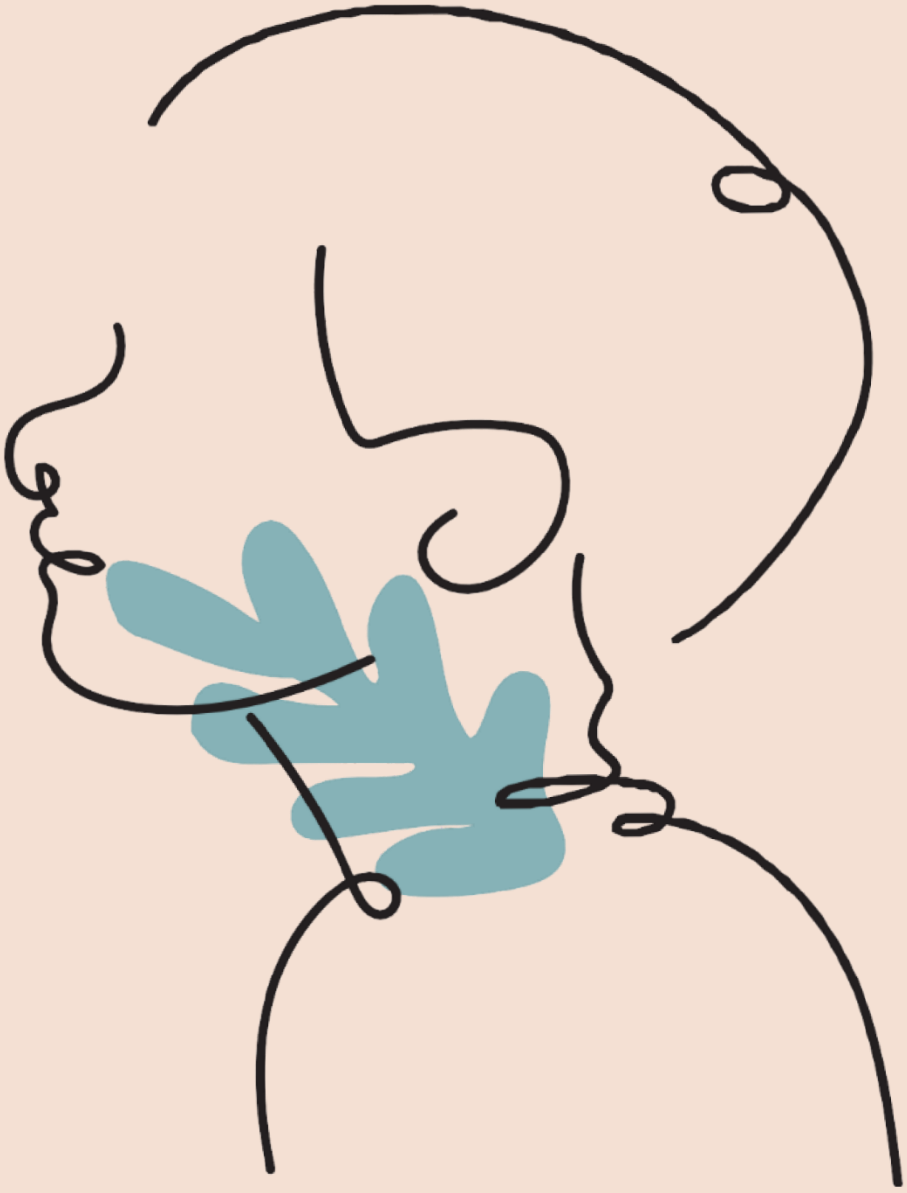
Aan mijn familie



General introduction

CHAPTER 1.

BACKGROUND

Since its first description by the French stomatologist Robin in 1923, Robin sequence (RS) has been extensively studied. The condition is characterized by a typical triad of symptoms, including a small mandible (mandibular hypoplasia), backward placement of the tongue (glossoptosis) and a varying degree of upper airway obstruction (UAO) (1-3) (**Figure 1**). Despite the numerous reports in literature, RS remains a complex and poorly understood condition. The interaction between the various etiological causes, the great variability in clinical expression, and the lack of a uniform definition continuously pose challenges to clinicians (4, 5). The following part of this chapter will discuss the background and the clinical implications of RS. At the end of this introduction, the aims and outline of this thesis will be presented.

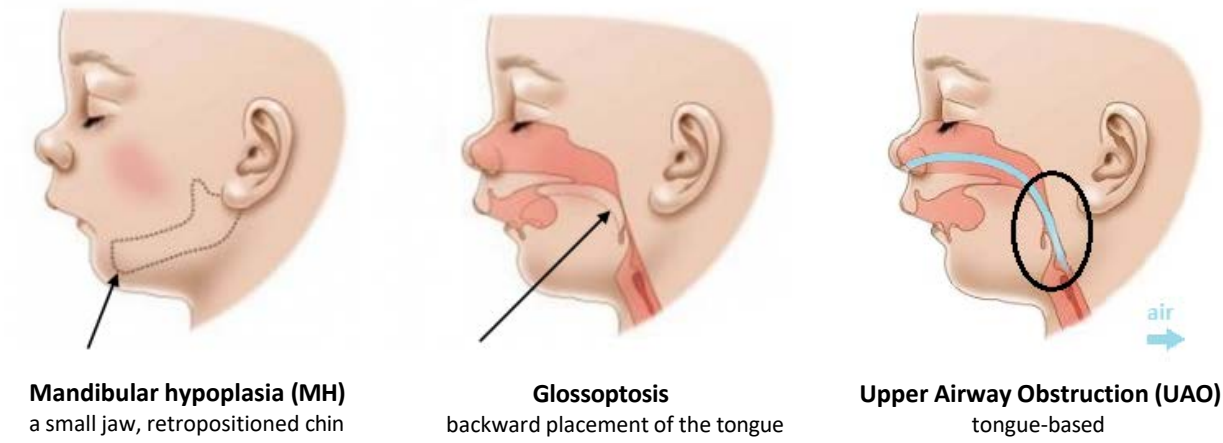


Figure 1. Pathophysiology of Robin Sequence
Typical triad of Robin Sequence: a small jaw (mandibular hypoplasia), backward placement of the tongue (glossoptosis), and a varying degree of upper airway obstruction (UAO)

HISTORY

The first reports in which the presence of micrognathia was described were those of St-Hillaire in 1822, Fairbarin in 1846, and Shukowsky in 1911 (6). RS owes its name to the first one who highlighted the serious consequences of the disease in 1923. Pierre Robin was a French stomatologist who described the triad of symptoms; micrognathia, glossoptosis, and upper airway obstruction (UAO), which he called the Pierre Robin syndrome (1). After 50 years, the validity of the word “syndrome”, which signifies a combination of symptoms with one particular cause, was questioned as it became clear that the etiology of the disease was heterogeneous. In the following years, several suggestions on definitions and nomenclature had been proposed. Hanson and Smith (1975) and Cohen (1976)

suggested the more thorough term Robin “anomalad’, which is used to describe a complex of symptoms with unknown etiology that can be part of (various) syndrome(s) but can also occur in isolation (7, 8). In 1978, Cohen came up with the word Robin “malformation complex”, indicating that each malformation is “nonspecific” and “facultative”; as it can occur in a wide range of syndromes and not all malformations may be expressed in each patient. For this reason, “the Robin complex is now known to be nonspecific, occurring *sui generis* or as a component of various syndromes” (9). In 1982, Smith introduced the term Robin “Sequence”, which indicates that a primary anomaly, here micrognathia, causes subsequent second and third abnormalities: glossoptosis and UAO (10). The first report on the presence of a cleft palate in combination with micrognathia was described by Fairbairn (1846) and was later referred as the Fairbairn Robin Triad (FRT) (11). In the next century, the association between micrognathia and the cleft palate was described by Lannelongue and Menard (1891), Shukowsky (1911), and Eley (1930) (12, 13). In 1934, it was the same Robin who first mentioned that a cleft palate can also be present as part of the triad and that it can seriously aggravate symptoms in these patients.

DEFINITION & DIAGNOSIS

There is a lot of controversy on the characteristics that include RS, causing a lack of a uniform definition of RS in literature. Using the same, widely accepted, definition is crucial for a thorough understanding in the communication between clinicians. Furthermore, the use of a uniform definition enables to collect and analyze data in a more standardized way and will therefore improve the comparability of outcomes within and between various centers. The challenge in the definition of RS lies in the fact that it is a clinical condition, with unknown etiology, defined by a combination of clinical characteristics that are hard to objectify. As the word “sequence” implies, it is believed that one primary characteristic causes various subsequent characteristics. These clinical characteristics, however, are considered to be “nonspecific” and “facultative”: severity of clinical symptoms can vary substantially and not every symptom may therefore be (visibly) expressed in each individual patient. Forasmuch as the exact etiology is still not determined, RS remains a summary of subsequent clinical characteristics with varying composition that can change in severity (over time).

The ambiguity of the definition is reflected in RS literature. Although not included in the original definition of Robin et al., various centers and studies included a cleft palate as the prerequisite of the triad, whilst the presence of UAO was not always necessary for diagnosis (14, 15). A disadvantage of

including a cleft palate as part of the triad is that it excludes the ± 10% of patients with MH and clinical characteristics of UAO who do not present with a cleft palate. Other studies considered feeding difficulties instead of breathing problems as part of the diagnosis (14). In this thesis the definition from the consensus meeting for Robin Sequence is used; mandibular hypoplasia, glossoptosis, and upper airway obstruction, with or without a cleft palate (3).

There is not only controversy on what characteristics should be included, but also within the definition of each characteristic. For the primary characteristic, some studies advocate the use of the word retrognathia whilst others prefer micrognathia. It is believed that micrognathia describes a hypoplastic mandible, often with a disturbed growth potential, whereas retrognathia refers to an abnormal mandibular position in patients with normal mandibular growth (14). Differentiating retrognathia and micrognathia seems hard since there is no data on mandibular volume and morphology in clinical findings. Inasmuch as the primary goal of this thesis is not to create a better and universally accepted definition, but rather to create a better understanding of the clinical implications of this condition and the challenges that go along, we decided to use the umbrella term. For this reason, we used mandibular hypoplasia (MH) throughout this thesis.

Despite that it is not considered as part of the diagnosis, a cleft palate is present in the majority of patients, with prevalence rates up to 90% (16-18). As with differences in nomenclature of MH, there is also a distinction in the description of a cleft palate. Some studies and centers suggest that the cleft palate is U-shaped whereas others advocate that the cleft can be V-shaped as well. The difference is believed to arise in the etiology: a primary malformation (V-shaped) or a consequence (U-shaped) of the Robin sequence caused by fetal tongue position between the palatal shelves due to limited space, preventing palatal closure (19-21). In this thesis we did not distinguish between types of cleft palates.

Besides the lack of a uniform definition in literature, another complexity in RS is the (objective) diagnosis. One of the difficulties in diagnosing RS is that it can be caused by multiple factors. Probably even more challenging is the heterogeneity of this disease that is not only pathogenically different but also phenotypically different: the same genetic mutations can result in various clinical features with variable degree of clinical expression whilst, conversely, different genetic causes (even in the same syndrome) may result in the same clinical features (4, 5). Hence, RS remains a cluster of symptoms with a variety of clinical expression in each individual patient. As long as the exact etiology is not elucidated, diagnosis is still based on the collection of presenting (visible) symptoms. For this reason, each clinical feature should be diagnosed independently.

EPIDEMIOLOGY

The incidence rate of RS ranges from 1/3120-1/122.400 live births, with a median prevalence of 1/14.500 (22, 23). This wide range is thought to be a consequence of the lack of a uniform definition that is used across studies and the inclusion of different (ethnical) populations. The different times when the studies were performed and various diagnostic modalities and criteria that have been used, further contribute to this varying incidence rate. The highest incidences are reported in recent studies, performed in wealthy countries, where there are many opportunities to use and perform diagnostic tools, increasing the chance to diagnose and report RS.

Mortality rates range from 2-26%, with an increasing rate in patients that present with other abnormalities (e.g. cardiac abnormalities, central nervous system anomalies) or a syndromic status (24, 25). Only a small percentage of deaths is directly attributable to respiratory obstruction (26). Over the last decades, mortality rates decreased due to improved diagnostic modalities, including genetic testing and examination of concomitant (cardiac and neurological) abnormalities, an increased availability of resources, and therefore a more personalized treatment approach (25, 26). The Dutch mortality rate is estimated to be 10% (24).

GENETICS

Robin sequence may occur in isolation (isolated RS) but can also be present in combination with other anomalies or a syndrome (non-isolated RS). Although various syndromes and genetic mutations have been associated with RS, no specific mutation is found to be the direct cause. The SOX9, SOX11, MAP2K6, KCNJ2&16, and BMPR1B genes have been described to be involved in craniofacial, and more specifically, mandibular development. Mutations in these genes are suggested to be the possible cause of RS (26-31). Moreover, mutations in the regulating genes, noncoding disruptions upstream or downstream of the gene, and enhancer deletions have also been reported to be the cause of disturbed mandibular growth (28). Depending on timing and/or location of these pathological disruptions in the genetic pathways, various phenotypes can occur and a wide range in clinical expression has been described (26, 27, 32). Forasmuch as many disease-specific genes may not have been identified yet, it remains unclear whether these genetic mutations are the singular cause of RS or that they should be considered as an associated finding.

ISOLATED RS

Patients who solely present with the core characteristics of RS can be categorized as **isolated-RS** (33). Depending on whether up-to date genetic testing is performed, isolated RS can be further subdivided into either "confirmed isolated" or "presumed isolated" (33). One should take into account that when updating the diagnostic modalities and tests in future and by identifying new disease-specific genes, some patients or diseases can become part of another category or syndromic spectrum.

NON-ISOLATED RS

The clinical features of RS can also be present in combination with additional comorbidities or a syndrome (non- isolated RS), that are present in around 60% of the cases with RS (27, 33-35). Over 40 syndromes and more than 40 (candidate) genes have been described to be associated with RS (36). Non-isolated RS can be further subdivided into two groups: **syndromic RS** and **RS-plus** (33).

Syndromic RS

If a syndrome is genetically confirmed or clinically strongly suspected, patients can be classified as **syndromic RS**. Syndromes that are most frequently associated with RS are presented in **Table 1**.

RS-plus

Patients are classified as **RS-plus** if they present with additional abnormalities that are not (yet) related to a currently known syndrome, even after consultation by a clinical geneticist and/or after up-to date genetic testing (20, 27, 33). The most common craniofacial abnormalities found in this subgroup are hypertelorism, low-implanted ears, and pre-auricular skin tags (33). Extra-craniofacial abnormalities that frequently occur are musculoskeletal abnormalities, ocular anomalies, and central nervous system anomalies (e.g. epilepsy, cerebral palsy) (33).

The various syndromes associated with RS and the broad variation of clinical symptoms that are found within the spectrum of RS, ranging from connective tissue disorders in patients with Stickler syndrome to multiple skeletal and soft tissue abnormalities in patients with (a form of) facial dysostosis, indicate the wide phenotypic and genotypic variability of RS and the many pathways that are involved. Moreover, clinical presentation may vary considerably within the same syndrome (4, 5). The combination of the heterogeneity in etiology and the wide variability in phenotype that is present within the RS population accentuates the complexity of this condition that continuously poses challenges to clinicians.

Table 1. Most common forms of syndromic RS

Diagnosis	Incidence	Inheritance	Genetic Mutation(s)	(Cellular) pathway affected	Clinical symptoms
Stickler syndrome	1:7500-9000	AD / AR	COL2A1, COL9A1, COL9A2, COL9A3, COL11A1, COL11A2	Procollagen biosynthesis (Collagen connective tissues type 2 and 11)	Ophthalmological disorders (e.g. myopia), micrognathia, (sensorineural) deafness, and articular manifestations (arthritis), spondyloepiphyseal dysplasia
Auriculocondylar	<1:1.000.000	AD / AR	PLCB4	Endothelin 1 signaling that regulates	Typical triad of :
syndrome (ACS)			GNAI3	expression of Distalless homeobox (DLX) transcription factors in neural crest cell development in the pharyngeal arches 1 & 2	• Micrognathia • Mandibular condyle hypoplasia • Question mark ears Other: Microstomia, palatal anomalies, glossoptosis, crowded teeth, full cheeks, post auricular tags, hearing loss, and facial asymmetry
TARP syndrome	<1:1.000.000	X-R	RBM10	RNA binding processes regulating alternative splicing (AS) of multiple different genes, inhibiting cell proliferation, promoting apoptosis, controlling cell division and replication	Mandibular hypoplasia, club feet, atrial septal defect, persistent left superior vena cava
Velocardiofacial(VCF) syndrome (22q11-deletion syndrome)	1:3800-6000	AD	TBX1 gene on 22q11.2	T-box transcription factor, essential for the development of (normal) pharyngeal arch arteries.	Cardiac outflow tract deformities, thymus and/or parathyroid gland hypoplasia/absence, hypocalcaemia and very characteristic facial dimorphisms, also known as the conotruncal anomaly face, including prominent nose with squared nasal root, narrow palpebral fissures, a nasal voice (which is often associated with the presence of a cleft palate)
Cerebrocostomandibular syndrome	<1:1.000.000 ****	AD / AR	COG1	Glycosylation	Micrognathia, mental retardation, posterior rib defects (range; total absence of ossification to (small) gaps in ribs)
			SNRPB	Spliceosome components that are crucial for processing pre-mRNA to mature mRNA	

Cornelia de Lange syndrome	1:80.000	AD / X-R	NIPBL, SMC1A, SMC3	Cohesin pathway involved in DNA repair, chromatid cohesion, and gene expression	Synophrys, concave nasal ridge, upturned nasal tips, thin downturned upper lip, upper-limb defects (hand oligodactyly and/or adactyly, hirsutism, growth retardation
Van der Woude syndrome	1:35.000-100.000	AD	IRF6	Transcription factor regulating proliferation and differentiation of epithelial cells in craniofacial midline formation during embryogenesis	(Congenital) lower lip pit, cleft lip and/or cleft palate, and hypodontia (missing second premolars)
Facial Dysostosis				**Neural crest cell formation of pharyngeal arches 1-4**	**Craniofacial features, with or without limb deformities** • without = *mandibulofacial dysostosis* • with = *acrofacial dysostosis* <u>Craniofacial features:</u> mandibular and/or maxillary hypoplasia, choanal atresia, cleft lip/palate, hypoplasia of the zygomatic complex, coloboma of the lower eyelids, ear defects (microtia, often associated with hearing loss)
Mandibulo facial dysostosissubtypes (MDBFD):					**Craniofacial features** **+** **additional, specific, characteristics per subtype:**
Treacher Collins syndrome	1:25.000- 70.000	AD / AR	TCOF1 , POLR1C, POLR1D	Ribosome biosynthesis; RNA transcriptions and RNA polymerase 1 and 3 complexes	Down slanting of the palpebral fissures
Burn McKeown syndrome	<1:1.000.000 **	AR	TXNL4A	Spliceosomal complex required for snRNP assembly and cell cycle progression	Cardiac defects, large protruding ears, short philtrum
MDBFD with microcephaly	<1:1 000 000 *	AD	EFTUD2	Spliceosomal GTPase that plays a regulatory role in catalytic splicing and post-splicing-complex disassemble	Microcephaly, cardiac anomalies, esophageal atresia, short stature, spine anomalies, intellectual disabilities, epilepsy

Acrofacial dysostosis (AFD) subtypes					Craniofacial features + Additional limb defects
					Pre-axial limb defects +
Nager syndrome	Unknown*	AR	SF3B4	U2SNP pre-spliceosomal complex which is one of a number of complexes that removes introns and ligates exons during splicing	Limb abnormalities, including radius aplasia, radioulnar synostosis, hypoplasia or aplasia of thumbs
Guion Almeida Syndrome	<1:1.000.000 *	AD	EFTUD2	Protein required for GTPase, involved in the splicing process and/or the recycling of spliceosomal snRNPs.	Progressive microcephaly, esophageal atresia, and psychomotor delay
					Post-axial limb defects +
Miller syndrome	<1:1.000.000 ***	AR	DHODH	Mitochondrial electron transport chain required for de novo pyrimidine synthesis	Accessory nipples, cup shaped ears, malar hypoplasia
Richieri-Costa-Pereira syndrome	<1:1.000.000	AR	EIF4A3	DEAD-box helicase, a core protein that is part of the exon junction complex	Microstomia, mandibular cleft, absence of central lower incisors, cleft palate, minor ear anomalies, laryngeal abnormalities (small round larynx, epiglottis hypoplasia/agenesis, microweb, hypertrophy of arytenoids and aryepiglottic folds, a fold in the posterior region of larynx and anterior movement of arytenoids), mesomelic shortening of upper and lower limbs (associated with short stature), hypoplastic thumbs/thenar/hypothenar, hypoplastic halluces, clubfeet, learning and speech impairment

***AD** = Autosomal dominant; **AR** = Autosomal recessive; **X-R** = X-linked recessive;*
**The exact prevalence is unknown; more than 100 cases have been reported;*
***Around 20 families reported in literature;*
****Less than 30 cases reported in the literature;*
*****Around 80 cases have been reported in literature*

CLINICAL FEATURES

RS is a very heterogeneous disease that can be caused by several etiologic factors. Nonetheless, the exact pathophysiology remains unknown. Hence, each clinical feature should be diagnosed independently.

MANDIBULAR HYPOPLASIA

PATHOPHYSIOLOGY

Inasmuch as mandibular hypoplasia (MH) is believed to be the primary characteristic of RS, three theories have been suggested to be on the basis of RS.

1. The **deformational theory** implicates that mandibular growth is intrinsically normal, but the MH occurs secondary to extrinsic factors that mechanically restrict mandibular growth, which is often the case in isolated RS patients (37, 38). These extrinsic factors can be:

- **Environmental determinants**: including maternal medication or maternal toxins.
- **Positional deformation**: abnormalities the in-utero environment and/or fetal position (e.g. uterine abnormalities, oligohydramnion, multiple fetuses, abnormal embryo implantation). Due to the reduced space, fetal neck extension, which normally occurs between the 6-12th week of gestation, is limited. As long as the fetal chin is compressed on the chest, mandibular growth is physically prevented (19, 36, 37, 39).

As soon as the restriction is resolved (after birth), these patients are believed to demonstrate normal mandibular growth, ending up with a physiologically normal mandible (19, 37).

Another hypothesis is that the MH is caused by intrinsic factors, which is often the case in non-isolated RS patients. The underlying pathologies of these intrinsic factors are often associated with a genetic mutation, which can be either chromosomal or a single gene defect. There are two theories that explain MH secondary to these intrinsic causes:

2. **Neuromuscular abnormalities theory**, caused by neurological dysregulation. Due to oropharyngeal hypotonia, myotonia, or disturbed neuromuscular signal pathway, the fetal head movements are inhibited, which subsequently prevents mandibular movements and head extension that are required for appropriate mandibular outgrowth (19, 36, 40). Moreover, tongue movements are inhibited and thereby mandibular growth and palatal shelve fusion are not stimulated, resulting in MH and a cleft palate (19).
3. **Malformational theory**, caused by abnormal migration and/ or formation of cranial neural crest cells (NCC). Most craniofacial structures are derived from NCC, and therefore, most craniofacial

deformities are caused by a disturbance in the organization of the NCC (41). Depending on the location, timing during development, and loss of function, various congenital abnormalities can arise. For example, defects in NCC differentiation may result in craniosynostosis (42), whereas disturbance of NCC formation and migration may cause phenotypes with hypoplastic jaws, ears, and/or a cleft palate, for example facial dysostosis (FaD) (43-45). Multiple genes and pathways may be involved, leading to underdevelopment of various craniofacial hard and soft tissues (46).

MANDIBULAR MORPHOLOGY & VOLUME

There is a broad spectrum of mandibular morphology and size. Compared to healthy controls, isolated RS patients have shorter mandibular ramus and body length, wider gonial angle, and a more posterior inclined chin, as found on radiographs, CT and MRI. In addition, mandibular bone is not only smaller, but also the volume of both the ramus and the body is hypoplastic, with a more obtuse symphyseal angle, and a steeper mandibular plane (3, 47-52). This often persists after childhood, as similar abnormalities are found in isolated RS adolescents (10-16 years) (49, 51).

Also within RS patients, mandibular morphology can vary considerably. Amongst isolated RS patients, 3 groups can be distinguished: a shorter mandibular body, both a shorter mandibular body and ramus, and a shorter mandibular body with a more obtuse mandibular angle (53). Moreover, compared to isolated RS patients, non-isolated RS patients have different mandibular morphology, size, and position that can also vary considerably between different syndromes (54-56). For example, patients with Stickler syndrome and 22q11- deletion syndrome are more susceptible to demonstrate similar mandibular morphology to that of isolated RS- patients but may have a more retropositioned mandible (retrognathia), whereas patients with facial dysostosis often have an aberrant mandibular morphology and a mandible that is also more hypoplastic (micrognathia) (4, 54). Lastly, there is also a broad spectrum of clinical variability within various syndromes. Some syndromic patients seem to have mandibular size (and morphology) that can approximate normal and that will not lead to functional airway compromise, whilst other patients with the same mutation may present with extremely deformed mandibles and severe functional complications (54-56). This further emphasizes both the etiological and clinical heterogeneity within RS patients.

A frequently discussed phenomenon in RS patients is the so-called mandibular “catch-up growth”. This theory suggests that mandibular growth during the first year(s) of life in RS patients is relatively faster compared to those of normal infants, resolving the mandibulo-maxillary discrepancy (57). Nonetheless, existence, timing, and whether this happens in all RS patients remains controversial (58). Underlying etiology, based on abovementioned theories (e.g.extrinsic factors versus intrinsic factors), is suggested to play an important factor (37, 54).

DIAGNOSING MH

Despite that it is considered as the primary characteristic of RS, diagnosing MH remains challenging. Various methods to assess and quantify mandibular size have been proposed, including cephalogram, CT, MRI, or direct measures on sight with rulers and calipers. Over the last decades, the use of CT and MRI has rapidly expanded. As it adds volumetric information to the morphologic data, the use of 3D-characterization has gained popularity. The radiation exposure, limited availability, high costs, and need for positioning and immobilizing the infant are substantial disadvantages and restrict (daily) use. Currently, no method is considered as the golden standard (57, 59). Another challenge in the diagnosis of MH is that there are currently no normative data on mandibles of (young) infants and a widely accepted classification system to characterize mandibular hypoplasia is lacking. Consequently, diagnosis of MH is mostly based on clinical evaluation on sight and therefore still largely subjective (3, 59).

GLOSSOPTOSIS

Glossoptosis is considered an important clinical feature in imposing UAO and feeding difficulties in RS patients (60-62). Besides that MH causes backward placement of the tongue, other factors can play a role in the presence and severity of glossoptosis in patients with RS. Normally, the genioglossus muscle is important to maintain protrusion of the tongue. By strongly increasing the tonic activity (phasic activity: periods of decreased activity, followed by bursting activity) during inspiration, this muscle prevents the tongue to fall backwards in the airway. A decreased tonic activity of the genioglossus muscle may result in glossoptosis due to its insufficiency to counteract against the gravity in supine position and the abrupt intrathoracic pressure changes during inspiration (63, 64). This decreased tonic activity can be caused by neurological dysregulation (62, 65). Moreover, since the mandible is hypoplastic, the surrounding soft tissues might be hypoplastic as well. This may include hypoplasia of the genioglossus muscle, causing too short or too tight genioglossus fibers that are less sufficient to actively position the tongue out of the pharyngeal airway (17, 66-68).

DIAGNOSING GLOSSOPTOSIS

Tongue size and position can be inspected via intra-oral investigation. A naso-endoscopy, however, allows a more precise visualization and is therefore considered a more adequate method to determine the presence and severity of glossoptosis (69). Other alternatives that have been proposed include dynamic CT or MRI. Radiation exposure and high costs are main disadvantages (70).

The challenge in the diagnosis of glossoptosis is that it is a dynamic entity. The severity of glossoptosis, the subsequent degree of respiratory obstruction, and the feeding difficulties may therefore vary considerably. Although several methods and classification systems have been proposed, they are associated with low sensitivity and poor reliability, as defined by poor to moderate inter- and intraobserver variability (71, 72). Furthermore, there is a weak association between current scoring systems and clinical severity of respiratory obstruction, leaving the diagnosis of glossoptosis largely subjective (71). Up till now, no method is considered as the golden standard to objectively and accurately diagnose and classify glossoptosis (71).

UPPER AIRWAY OBSTRUCTION

Upper airway obstruction (UAO) is defined as the respiratory distress that occurs secondary to an obstruction that can be present in the whole upper airway, independent of the state (awake or sleep). The spectrum of respiratory compromise in RS patients varies broadly. In severe cases, UAO may occur directly postpartum and often requires immediate intervention (endotracheal intubation or a tracheostomy). Most RS patients, however, are mildly affected (16, 73, 74). Although symptoms of severe UAO are often clearly evident and continuously present, symptoms of mild UAO can be more subtle. Generally, these clinical symptoms become more apparent during feeding or laying in supine position (3, 73). In addition, respiratory symptoms can also aggravate or even occur particularly during sleep, which is called sleep-disordered breathing (SDB) (3, 73, 75, 76). SDB is a complex phenomenon of increased upper airway resistance and/ or pharyngeal collapse causing respiratory compromise that specifically occurs during sleep (**Figure 2**). The clinical entities of SDB involve primary snoring, upper airway resistance syndrome (UARS), obstructive hypoventilation, and obstructive sleep apnea (OSA). When unrecognized and left untreated, SDB may lead to various comorbidities including failure to thrive, cardiovascular problems, affected quality of life, psychological problems, and in extreme cases sudden death (3, 76-79).

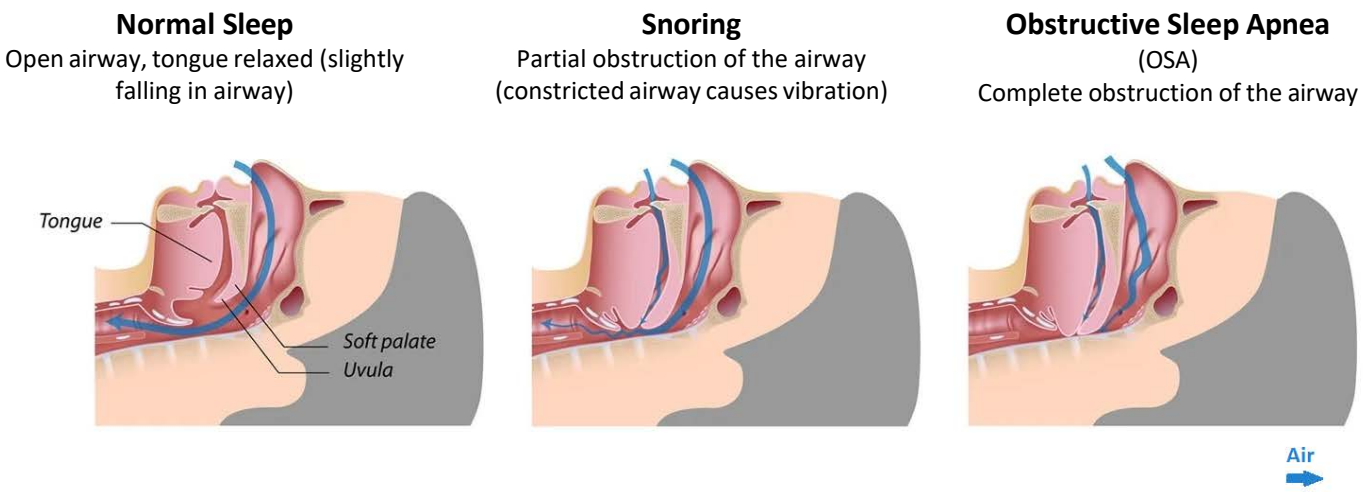


Figure 2. Spectrum of sleep disordered breathing

PATHOPHYSIOLOGY OF UAO

Normally, sufficient airway patency is provided by activation of the pharyngeal dilator muscles. In healthy children, airway resistance in the pharynx increases during sleep due to relaxation of the pharyngeal dilator muscles. By increasing tonic activity of these muscles during sleep, pharyngeal volume increases, which diminishes resistance in the pharyngeal airway. This counteracting mechanism, that is activated in case of increased negative pressure, decreased airflow, or increased CO2 levels, is regulated by a reflexive mechanism in the brain stem, based on the information of pharyngeal mechanoreceptors (80-82). In patients with UAO, airway patency is diminished. The extent of reduction of airway caliber is often correlated with the severity of obstruction, in which multiple pathological factors can interplay. First, anatomical factors may narrow the airway, including MH that causes the tongue to physically obstruct the airway. Subsequent anatomical airway abnormalities (e.g. adenotonsillar hypertrophy, choanal atresia, laryngomalacia) may cause or further contribute to the UAO in RS patients (69). Second, dysfunction of the (oro)pharyngeal muscles may result in airway collapse as they are not strong enough to work against the suddenly appearing intrathoracic negative pressure changes and/or gravity forces (63, 64, 83-85). Muscular dysfunction can be caused by hypoplasia of the involved muscles, but can also be caused by neurological dysregulation which can be either central or peripheral (83, 84).

DIAGNOSING UAO

An overnight, preferably in-laboratory, video (level 1) polysomnography (PSG) is considered the golden standard to objectify and diagnose UAO during sleep (**Figure 3**) (76, 77).

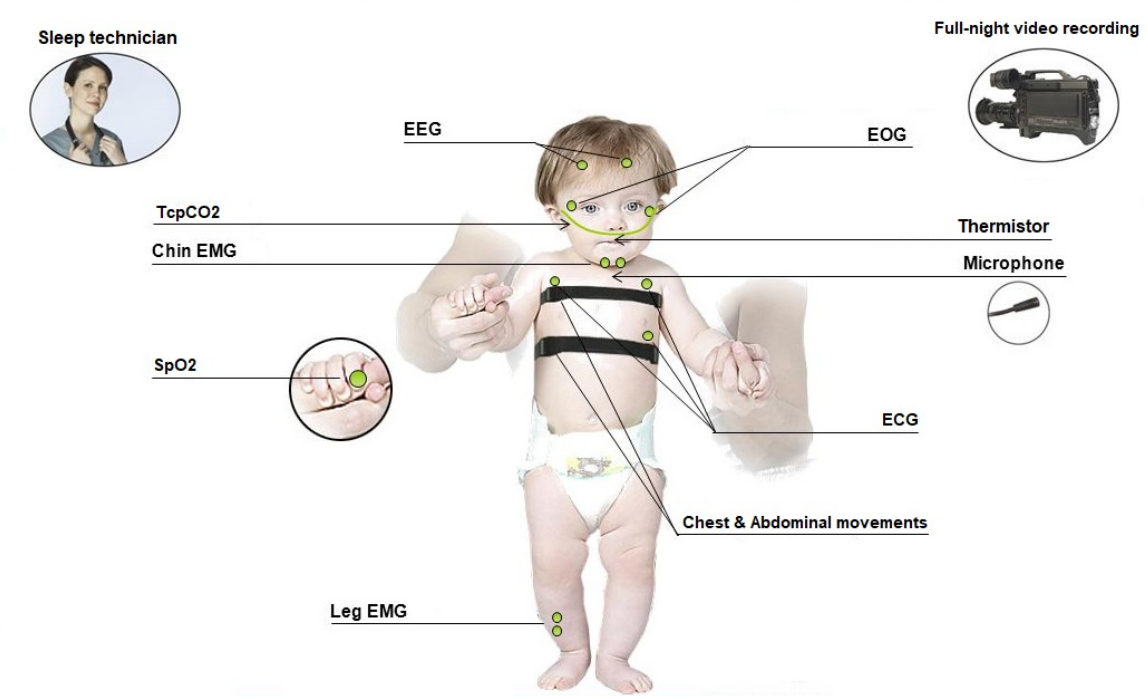


Figure 3. In-laboratory video polysomnography (level 1)
***EEG** = electroencephalogram, **tcpCO2** = transcutaneous partial pressure of carbon dioxide, **EMG** = electromyography, **SpO2** = Oxygen saturation in blood, using pulse oximetry, **EOG** = electro-oculography, **ECG** = electrocardiography.*

Besides diagnosis, it also assesses severity of obstruction, often expressed in an (obstructive) apnea hypopnea index (AHI). As it quantifies the severity of obstruction, a PSG can be very useful as a guide in choosing appropriate management strategies and clinical decision-making. Performing an in-laboratory PSG is not always feasible due to the lack of time or availability, especially in tertiary hospitals and in low- income countries. Efforts have been made to develop validated alternatives such as ambulatory or home- based PSG (level 2 ≥7 parameters; level 3, ≥4 parameters; & level 4, ≥1 parameters (e.g. oxygen saturation and/or airflow) (75, 86, 87). Another alternative is oximetry, which objectifies oxygen (de)saturation(s) (88). A commonly used measure in oximetry is the McGill oximetry score that takes into account number and severity (depth and duration) of desaturations. Despite the fact that a score above 1, which is considered abnormal, is correlated with a high positive predictive value (97%) for an AHI >1, the negative predictive value is much lower (53%) (88, 89). Although less reliable, sleep-related questionnaires have also been considered in the diagnosis of UAO (90-94).

VISUALIZING SITES OF OBSTRUCTION

Careful evaluation of the whole upper airway is required in patients with unexplained (persisting) UAO, especially those with non-isolated RS (69). By performing a naso-endoscopy the upper airway is dynamically assessed and different sites of obstruction can be visualized (**Figure 4**) (95-99).

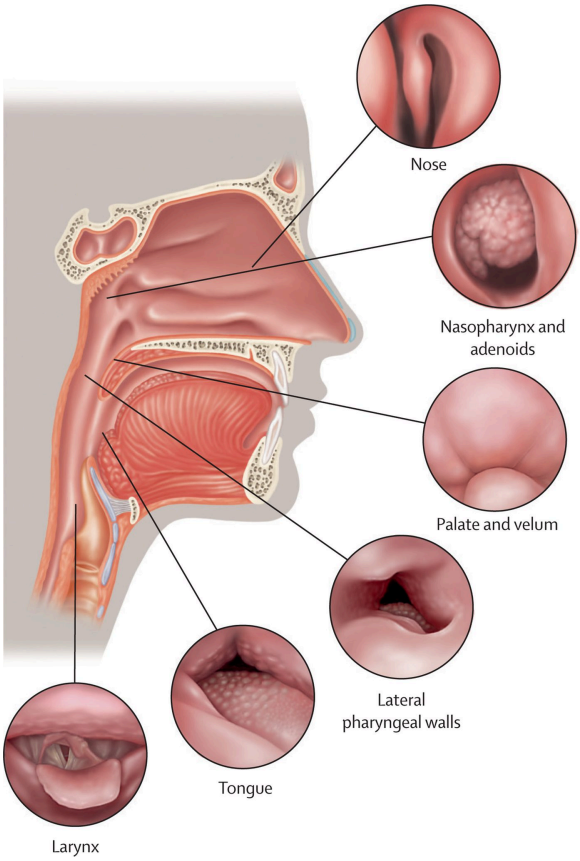


Figure 4. Possible levels of upper airway obstruction, visualized by a naso-endoscopy

By determining the site(s) of obstruction, outcomes of the PSG can be explained and treatment can be more targeted (100, 101). Other imaging modalities, such as (cine-)MRI and CT may be used in addition to the PSG and naso-endoscopy to determine the (concomitant) level(s) of airway obstruction (102). Radiation exposure, challenges encountered in the cooperation of infants, meticulous anesthetic administration, and technical difficulties prevent the extensive use in children (102, 103). In addition, to describe the view obtained by direct laryngoscopy and to assess the likelihood of a difficult orotracheal intubation, the Cormack-Lehane Score (CLS) is often used (**Figure 5**) (104).

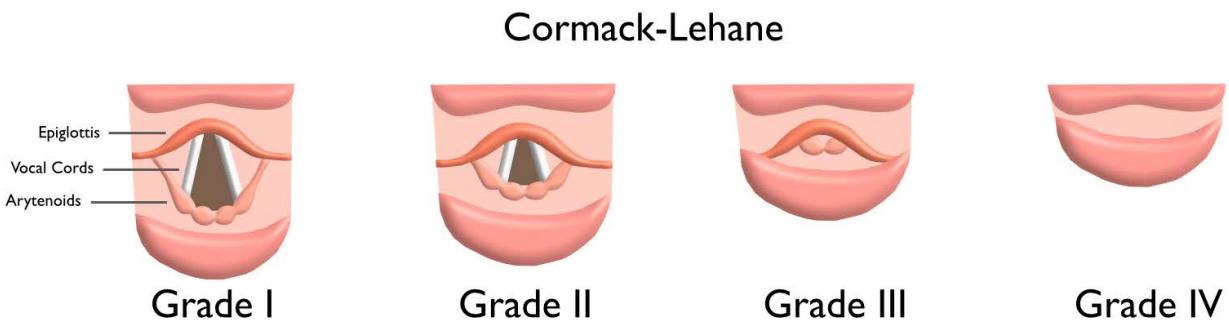


Figure 5. Intubation conditions, according to the Cormack-Lehane score

FEEDING DIFFICULTIES

Next to the respiratory compromise, patients with RS often present with feeding difficulties (FD) which are present in around 80% of the patients (105). Feeding difficulties in RS patients are characterized by increased feeding times (> 30 min), exhaustion during feeding, sleepiness, blue lips during feeding, coughing, gagging, and vomiting, often resulting in a diminished oral intake. The cause of impaired feeding function in these patients is often multifactorial, including anatomic tongue position, cleft palate, nasal regurgitation, gastro- esophageal reflux, and swallowing difficulties. Since FD are closely related to UAO, the FD can also occur secondary to the airway obstruction. The exquisite timing that is required and the increased effort to work against an obstructed airway may affect sufficient coordination of breathing, sucking, and swallowing (62). When inadequately managed, FD may lead to poor weight gain, growth impairment, and eventually failure- to-thrive. To prevent these (long-term) comorbidities, providing sufficient intake is crucial in these patients.

DIAGNOSING FEEDING DIFFICULTIES

Presence and severity of feeding difficulties can be defined in terms of the necessity of additional tube feeding (e.g. nasogastric tube, gastrostomy) (**Table 2**) (106). Secondly, growth, compared to the healthy reference population that is expressed in growth charts, can be used as a measure of (successfulness of) feeding abilities (107, 108).

Table 2. Classification of Feeding Difficulties

Classification	Severity	Description of FD
1	No - Mild	Patient can be fully orally fed, regardless of consistency or Feeding mechanism (i.e. Habermann bottle)
2	Moderate	Patient requires additional tube-feeding to acquire adequate intake
3	Severe	Patient is fully dependent on tube feeding

Classification of feeding difficulties according to Caron et al. (106). ***FD*** *= Feeding difficulties.*

SWALLOWING DIFFICULTIES

To facilitate successful feeding, a sufficient swallowing function is essential. The swallowing process is a complex mechanism consisting of a chain of rhythmically coordinated and reflexive movements of several oropharyngeal structures. Central pattern generators, located in the brainstem, control and coordinate the swallowing mechanism (107). The physiological mechanism of swallowing includes 3 phases; oral, pharyngeal and the esophageal phase (109) (**Figure 6**). The oral phase of swallowing can be subdivided in an oral- preparatory and oral-propulsive phase (109, 110).

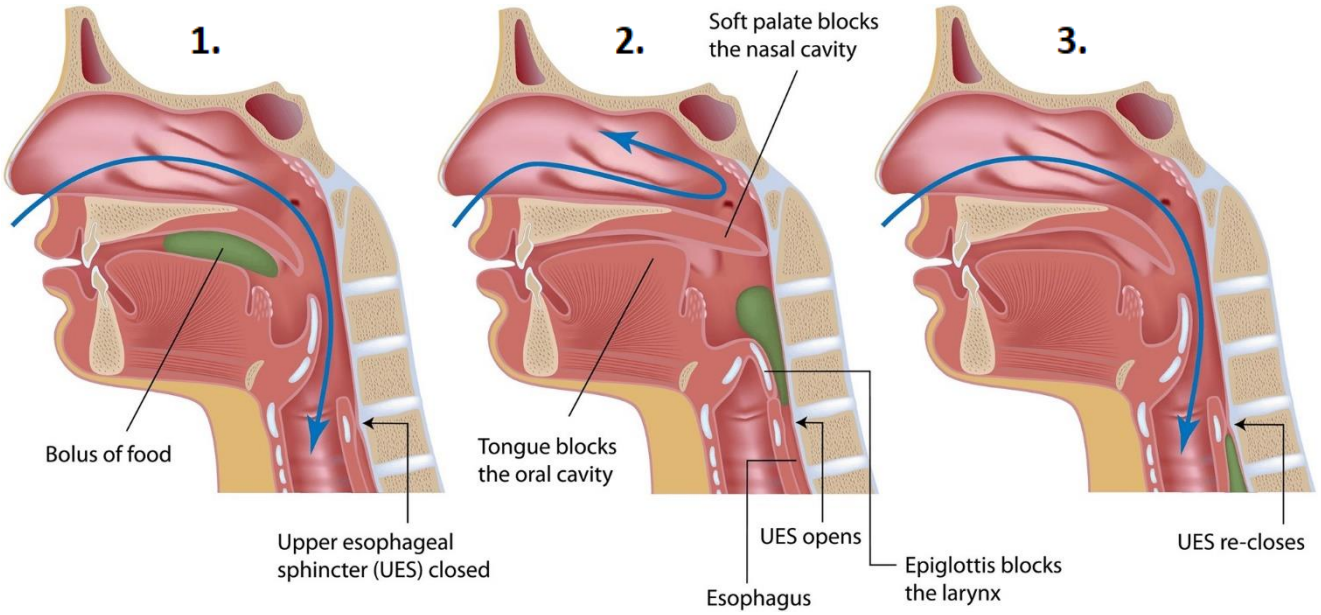


Figure 6. Phases of swallowing

***1** = oral phase of swallowing; **2** = pharyngeal phase of swallowing; **3** = esophageal phase of swallowing*

***UES** = Upper esophageal sphincter*

During the oral phase of swallowing, the bolus is formed and transported to the pharynx by voluntary movements of the tongue. Along with this transport, sensory receptors in the oropharynx are activated, which initiates the pharyngeal phase of swallowing. During the pharyngeal phase, contraction of the pharyngeal muscles stimulates further descending transport of the bolus from the pharynx to the esophageal sphincter. Throughout this strictly organized phase, several activities are performed in chronological order to provide a safe swallowing function: constriction of the upper pharynx and soft palate and subsequent elevation of the velum close off the nasopharynx from the oropharynx and hereby preventing nasal regurgitation. The elevation and anterior movements of the hyoid and larynx, the adduction of the vocal cords, the tilt of the arytenoids, and the descending of the epiglottis induce closure of the airway to prevent penetration and/ or aspiration.

The esophageal phase starts when the bolus arrives at the upper esophageal sphincter. Elevation and forward movement of the larynx to the hyoid induces the opening of the esophagus, followed by relaxation of the upper esophageal sphincter. Due to peristaltic movements and (normal) gravity forces, the bolus is further transported through the esophagus. At the end of the esophagus, relaxation of the lower esophageal sphincter allows the bolus to enter the stomach (107, 109, 110).

Normally, the greatest advancements in the (development of) feeding and swallowing skills take place during the first year of life. In the first postnatal months, the sucking and swallowing mechanisms predominantly consist of automatic movements and reflexes. Around the age of 3-4 months, the development of lateral tongue movements is initiated and bolus manipulation is introduced (107, 111). From the age of 6 months onwards, the swallowing mechanism becomes more and more voluntary as the mastication starts due to maturation of cortical afferent neurons (111, 112). During this phase, transition of feeding skills is initiated by the introduction to spoon feeding (107). Around the age of 1 year, adequate development of the voluntary feeding skills has been reached and sucking patterns are minimized. From this age onwards, children generally no longer use the sucking mechanism and the transition to cup drinking and spoon feeding is finalized. By the age of 2 years, the infant has developed lateral tongue movements and motor chewing skills have become more rotary so that the processing of food becomes more and more effective (107, 111).

To provide a safe swallowing function, accurate muscle function and precise neuromuscular coordination and timing between the participating structures are required (111). Since it is such a complex system, involving multiple signal pathways and structures, this system is prone to disturbances during development. In normal patients the respiratory and digestive tract are separated at birth, allowing the neonate to both breathe and feed safely. As the child gets older, the pharynx lengthens vertically and the contact of the epiglottis with the soft palate disappears as the length of the neck increases, resulting in a lower position of the larynx. Eventually, at the age of 2-3 years, the pharynx becomes part of both the digestive and the respiratory tract, which makes children from this age vulnerable for aspiration (109, 111).

Patients with MH are at an increased risk for the presence of swallowing difficulties (111, 113). In these patients, dysphagia can result from a wide range of functional or structural deficiencies. Anatomical abnormalities include MH, which causes limited tongue movements due to a reduced anatomical oropharyngeal space, a cleft palate, adenoid/tonsillar hypertrophy, and problems with chewing due to malocclusion (109, 114, 115). Besides these anatomical deficits, disturbed sucking and swallowing mechanisms may also be caused by muscular dysfunction. Hypoplasia of the (oro)pharyngeal muscles causes a less powerful, and hereby, less efficient swallowing function (116). This may include hypoplasia of the genioglossus muscle, causing too short or too tight genioglossus fibers that are less sufficient to actively position the tongue out of the pharyngeal airway and to perform adequate lingual movements (66, 67, 116). Neurological dysregulation at the level of the central nervous system may cause neuromuscular dysfunction and/or discoordination of the neuro-motor complex of swallowing. Nuclear lesions in the brainstem (pons and medulla) and corticobulbar pathways can result in denervation of the oropharyngeal muscles (116-118). In these patients, other neurological deficits, including mental retardation, are often present (116). In patients with RS, however, it is suggested that swallowing difficulties can also be caused by isolated dysregulation of the central pattern generator of the swallowing mechanism, causing disturbed coordination, without any structural changes of the cranial nerves and/or nuclear pathways (84, 116). Lastly, an increased work of breathing, tachypnea, GERD, laryngo- and/or tracheomalacia, and the presence of a tracheostomy tube, which is often present in patients with severe MH, can negatively affect feeding and/or swallowing mechanisms (3, 110, 111, 119).

CLEFT PALATE

Although not a prerequisite for the diagnosis, a cleft palate occurs in up to 90% of the patients with RS (3, 17). Patients with a cleft palate have an increased risk of developing feeding and swallowing difficulties (120). Due to the open palate, these patients experience difficulties in building up negative intraoral pressure, causing a weak sucking mechanism (121). By closing the palate, feeding skills and sucking patterns may improve (122). However, patients with RS are at an increased risk to develop airway-related complications following cleft palate repair due to the decreased oropharyngeal space (123, 124). In order to minimize these complications, it is suggested to postpone cleft palate repair in children with RS, giving the infant and its airway time to (absolutely) grow. Nonetheless, timing of ideal CP closure remains debated due to the fact that closure is also necessary for proper feeding, swallowing/sucking, and speech development (108).

DIAGNOSING SWALLOWING DIFFICULTIES

Various examinations can be performed to examine the presence and nature of swallowing dysfunction. The assessment of swallowing function starts with the evaluation of a specialized speech and language therapist (SSLT). After an anamnesis, the SSLT evaluates the feeding abilities, oral motor skills (nutritive and non- nutritive), and safety of swallowing during the intake of foods and liquids of different consistencies, according to IDDSI framework (**Figure 7**) (125).

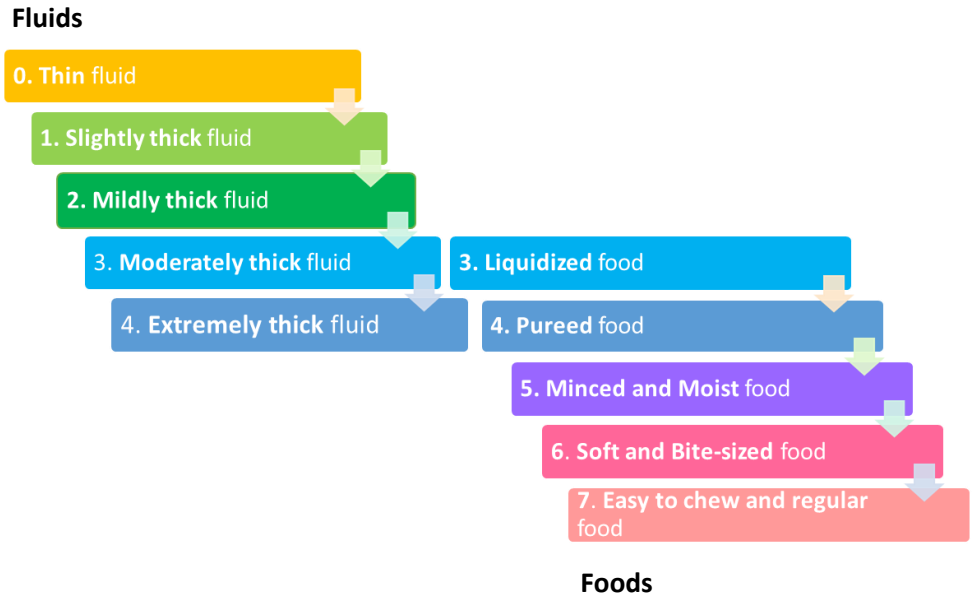


Figure 7. Foods and liquids of different consistencies, according to the IDDSI framework

To systematically assess the feeding and swallowing function, various observational scales and checklists can be used (126-129). Cervical auscultation by a stethoscope can be used to identify penetration/aspiration in liquid foods (130). In patients with a tracheostomy tube, a Modified Evans Blue Dye Test (MEBDT) can be performed to quickly and easily screen for an insufficient swallowing function (131). In case of (high) suspicion of swallowing dysfunction, additional diagnostic tools can be utilized to objectify the presence and nature of swallowing difficulties. A video fluoroscopic swallow study (VFSS), performed by a radiologist and SSLT, dynamically assesses the functionalities of the swallowing mechanism by recording fluoroscopic images during the intake of a radio-opaque bolus. This investigation enables a precise evaluation of the different phases of swallowing during the intake of different consistencies (e.g. thin liquid, thick liquid, pureed, and solid foods) (110, 132, 133). Although the patient is exposed to radiation, VFSS is assumed to be relatively safe in terms of radiation exposure risks (134). A Fiber-optic endoscopic evaluation of swallowing (FEES), usually performed by a pediatric otorhinolaryngologist, (solely) assesses the pharyngeal phase of swallowing by visualizing laryngeal function and glottic capability using a flexible scope (126, 135).

As VFSS and FEES have been demonstrated to have a high sensitivity of detecting penetration and/or aspiration and have been administered to manage patients with dysphagia in different patient populations, both methods can be considered as the golden standard (135, 136). Electromyography (EMG) can also play an important role in the evaluation of swallowing function. Forasmuch as it assesses the neurologic function of the orofacial structures, including the brainstem and the involved cranial nerves, EMG is able to differentiate between the various causes of dysphagia (116). Furthermore, severity can be determined and therefore the potential duration of swallowing disorders can be estimated (116). Lastly, it is capable to uncover swallowing abnormalities, even in cases of a seemingly sufficient swallowing function. However, performing EMG in infants is challenging due to technically difficulties and the cooperation of the child that is required (137).

MALNUTRITION AND GROWTH

Malnutrition is defined as the imbalance between the nutritional requirements of a patient and the intake, and includes underweight (low weight for age), wasting (low weight for height), and stunting (low height for age) (138). Multiple factors can cause or aggravate malnutrition: altered nutrient utilization, decreased nutritional intake, increased nutritional requirements, or increased nutrient losses. RS patients are prone to endure malnutrition (62, 139). The combination of the aforementioned increased energy expenditure that is required to breathe against an obstructed airway in combination with increased metabolic rates in RS patients, enhance the energy requirements. The limited intake due to FD and SD may further increase the risk of (aggravation of) malnutrition in RS patients (140). The presence of malnutrition is associated with several comorbidities due micro- and macronutrients deficiencies, including increased infection rates, wound healing problems, and an increased length of hospital stay (138, 141). Furthermore, inadequately treated acute malnutrition (< 3 months in duration) may eventually result in chronic malnutrition (>3 months in duration), that negatively affects growth during pediatric development and can lead to failure to thrive and poor developmental outcomes (138, 139, 142).

DIAGNOSING MALNUTRTION AND FAILURE TO THRIVE

Nutritional status (e.g. malnutrition) can be reflected in individual growth by using calibrated growth charts (143). Based on accurate anthropometrical measurements, individual growth can be visualized and compared to published (national) standards, expressed in standard deviation scores (SDS) (143). Depending on the child's age, several types of malnutrition can be defined (**Table 3**) (144).

Table 3. Definitions of malnutrition

Type of malnutrition	Criteria
Acute malnutrition	
Age < 1 year old	WFA <-2 SDS
Age 1 - 21 years old	WFH <-2 SDS
Chronic malnutrition	
Age 0 – 21 years old	HFA <-2 SDS
Age < 4 years old	HFA deflection of > 0.5 SDS within 1 year

WFA = weight-for-age. HFA = height-for-age. SDS = standard deviation score based on published standards of the Dutch reference population (13).

MANAGEMENT

TREATMENT OF UAO

NON-SURGICAL TREATMENT

In the majority of patients (around 90%) conservative, non-surgical, methods are sufficient in creating a permissible airway during the first months of life, allowing the absolute growth of the neonatal airway and improvement of clinical conditions (16, 73, 74). Furthermore, the immature neuro-motor system of the breathing mechanism gets time to adequately develop (84, 145).

Positional Therapy:

Most algorithms start with positional therapy (PT) to see whether respiratory distress dissolves, which seems to be the case in 40-70% of the children (17, 146-148). The mechanism is that by prone or side position, gravity enforces a change of mandibular and hereby tongue position in forward direction, preventing the tongue to physically obstruct the airway. Disadvantages of prone positioning are its association with an increased risk of sudden infant death syndrome (SIDS) and that signs of respiratory difficulties are less visible in this position (26, 149). Lastly, there seems to be a chance that UAO still persists after treatment with PT, even if clinical monitoring demonstrated that UAO was relieved (150). Therefore, monitoring is often indicated when neonates are sent back home (151).

Orthodontic / Tubingen plate

Another (potential) method that prevents the tongue to fall back into the upper airway is a customized orthodontic plate. The conventional plate is placed in the oral cavity, covering the entire hard palate and dentoalveolar ridge (152). In this way, the plate flattens the tongue, and thereby, glossoptosis and the penetration of the tongue in the nasal airway is prevented. Moreover, the appliance is believed to simplify sucking and swallowing mechanisms, subsequently stimulating adequate feeding (26). Later, an advancement was made on the oral appliances by lengthening the velar extension (also known as the Pre- Epiglottic Baton Plate (PEBP)) (153). In this way, the tongue base is placed more anterior, increasing the hypopharyngeal airway space. A disadvantage of the plate is that, as the child grows, the oropharyngeal anatomy alters as well and therefore daily to weekly adjustment of the personalized plates is necessary.

When repositioning the tongue by non-invasive methods is not effective in relieving respiratory distress, other non-surgical methods can be considered.

Nasopharyngeal airway (NPA)

In case of persistent tongue-based UAO despite non-surgical positioning of the tongue, a nasopharyngeal airway can be placed (154). Under radiographic or endoscopic evaluation, the tube is placed via one of the nostrils just above the epiglottis. In this way, the oropharynx is bypassed. This temporary method is used for several weeks to months to give the neonate and its airway time to grow and the neuro-motor system the opportunity to adequately develop. Furthermore, sufficient respiratory effort is generated during feeding, promoting adequate feeding and weight gain (145). Disadvantages include obstruction of the tube (e.g. mucus secretions), aspiration of gastric substances and the prolonged hospital stay or intensive home management (145, 155, 156).

Continuous Positive Airway Pressure (CPAP)

Continuous positive airway pressure provides positive pressure during both the inspiration and expiration of a breathing cycle. By constantly increasing the pressure, CPAP keeps the airway open, preventing upper airway collapse, supporting alveolar gas exchange, and in this way improving oxygenation. CPAP is often considered in patients with moderate-severe UAO and can serve as a (temporary) bridge to contemplate more definite, surgical, intervention(s). The disadvantage is that children need to wear nasal masks, which can be challenging for young children with uncooperative behavior. Furthermore, as the mask needs to be customized and fully fitting to prevent the leakage of air, several adjustments on the mask need to be made over time (22, 150).

Oxygen supplementation

During oxygen supplementation, oxygen is administered in a greater concentration than is present in ambient air. In this way, it has a beneficial effect on oxygen saturation levels to prevent hypoxemia and its concomitant comorbidities. As for CPAP, oxygen supplementation is a temporary solution that can be effective in the management of moderate UAO (157). Oxygen therapy is indicated in patients who demonstrate desaturations and/or hypoventilation, but who do not directly require invasive surgical interventions, or in patients in whom CPAP is contraindicated (157, 158). Long-term oxygen supplementation, however, may cause hyperoxia, which can cause several comorbidities including cell damage and cell death, pulmonary toxicity, and negative effects on the central nervous system (159).

High Nasal Oxygen Flow Cannula (HNFC)

With the addition of sufficient warmth and humidification to the breathing gas, high nasal oxygen flow cannula (HNFC), also known as Optiflow, allows higher flow rates compared to normal nasal cannula devices. In this way, it improves alveolar gas exchange by increasing the conductance and pulmonary compliance (compared to dry, cooler gas), reducing the nasopharyngeal dead space, and reducing the metabolic work associated with gas conditioning. Additionally, by providing adequate flow, inspiratory resistance (work of breathing) is reduced, which is considered less invasive compared to CPAP (160, 161). Other advantages include its ease of use, better tolerance in children (e.g. less damage to skin, reduced rates of nasal trauma, lower sense of dry nasal or oral mucosa, and reduced infant pain scores) and bigger comfort for caretakers and parents (161). Nonetheless, considering the disadvantages, including the lack of monitoring for the level of extending pressure in HFNC and the (dangerously) fluctuation of pressure because of leaks through the mouth and nasal passages, careful monitoring at an intensive or intermediate care setting is highly recommended (161, 162).

Endotracheal Intubation

Endotracheal intubation can provide a safe airway in cases with immediate and severe obstruction. By placing a tube, the airway is kept open to support oxygenation. It can serve as a temporary measure to promote maturation of the breathing pattern and give the airway time to grow. In this way, (long-term) invasive intervention is delayed or may even be avoided. Nonetheless, despite that some patients profit from endotracheal intubation, intubation is a risk factor for more invasive, surgical intervention in the majority of patients (16, 163-165).

SURGICAL TREATMENT

Surgical treatment is often indicated for severely affected, predominantly non-isolated, patients in whom mandibular growth and position are unlikely to normalize (16, 73).

Glossopexy/ Tongue Lip Adhesion

Glossopexy is the overall definition of a surgical procedure to attach the tongue to the structures in the anterior part of the mouth. In this way, the tongue is pulled forward, preventing the tongue to obstruct the airway. In case of tongue lip adhesion (TLA), the tongue is attached to the mucous membrane and muscle of the lower lip by sutures, pulling the tongue forward and resolving the glossoptosis. The biggest disadvantage of this procedure is that it does not solve the primary defect in RS: mandibular hypoplasia (26). Hence, in patients with severe MH, without normal mandibular growth potential, other surgical interventions are (eventually) required. Another disadvantage is that this surgical procedure is associated with several complications, including dehiscence, infections, edema, and Wharton's ducts injuries (166, 167).

Tracheostomy

Since it bypasses the level(s) of obstruction, tracheostomy placement is considered a very effective method in creating a safe and permissible airway. Nonetheless, there are several disadvantages to this treatment. Firstly, it should be emphasized that it does not resolve the cause of obstruction (MH). In patients in whom the MH persists, other methods that treat the primary cause of the obstruction are often required (26). Secondly, the presence of a tracheostomy tube is associated with several comorbidities (e.g. tracheomalacia, swallowing dysfunction, chronic pneumonia, mortality related to mucus plugging, complex nursing, and diminished social interactions) (168-171). Lastly, it is associated with higher costs compared to MDO or TLA (172-174).

Mandibular Distraction Osteogenesis (MDO) (Figure 8).

Mandibular distraction osteogenesis (MDO) can be an effective method to provide an accurate airway, with success rates of up to 95% in isolated cases (175-180). The MDO procedure starts with an osteotomy of the mandible and placement of the distraction device, followed by a latency period of around 0-2 days. During the active distraction phase, the mandible is gradually lengthened. This induces a physiological regeneration process and the stimulation of new bone formation at both ends of the fracture, parallel to the distraction vector. Continuation of active lengthening of the mandible is

dependent on the functional outcomes that needed to be improved (enlargement of the oral pharyngeal airway space and/or to correct malocclusion (e.g. open bite, asymmetry)). After the intended length of the mandible is achieved, the distraction device is fixated for mineralization and maturation of the newly-formed mandibular bone and the surrounding soft tissues (181). A major disadvantage, as for all surgical procedures, is the risk of postoperative complications, including nerve damage, wound infections, development of scar tissues, premature consolidation, dental damage and/or damage of tooth germs, and potential temporomandibular joint ankylosis (177, 178, 182).

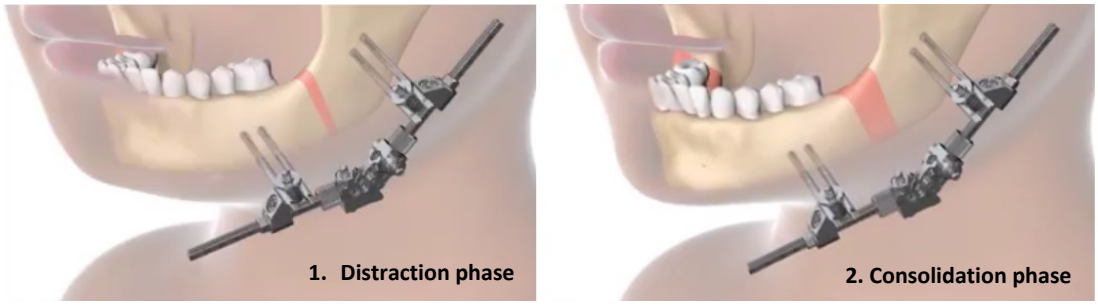


Figure 8. Mandibular Distraction Osteogenesis
1 *= beginning of mandibular distraction (distraction phase); and* ***2*** *= end of mandibular distraction (consolidation phase).*

MANAGEMENT OF FEEDING, SWALLOWING AND GROWTH

To support and simplify oral intake, RS patients often require other feeding mechanisms (e.g. Habermann bottle). Furthermore, since an adequate swallowing function is also necessary for sufficient oral intake, correct education and practice during the first year(s) of life is critical for a sufficient development and further improvement of feeding skills (111, 112). This can be guided by a specialized speech and language therapist. In patients with insufficient or unsafe oral intake, additional tube feeding or gastrostomy tube placement is required to provide adequate/proper intake and to maintain weight gain. Additionally, a dietician can be consulted to establish nutritional requirements and provide a schematic overview for sufficient intake to support optimal growth. Furthermore, since feeding difficulties are closely related to respiratory outcomes in patients with RS, it is believed that resolution of UAO may reduce the presence and severity of concomitant FD and SD and will improve weight gain (150, 183-186).

OUTLINE AND AIMS OF THESIS

The aim of this thesis is to set another step towards a better understanding of this complex and challenging condition by focusing on functional outcomes in patients with RS. By describing and evaluating the clinical symptoms that may occur in these patients, we endeavor to add valuable information to the current knowledge of RS and in this way contribute to an improved quality of care for these patients.

Mandibular Hypoplasia

In **Chapter 2**, a new, non-invasive, simple, and safe method using straight forward digital photography to assess mandibular length is presented. By differentiating RS patients to controls, we will endeavor to create more perspicuity on the role of MH in the diagnosis of RS. Furthermore, by evaluating patients longitudinally during the first 4 years of life, we will attempt to gain more insight on mandibular growth.

Functional outcomes after treatment

In order to improve management plans, we will evaluate outcomes following treatment in our center. In **Chapter 3**, an overview of patients who were treated non-surgically between 2011 and 2021 in our center will be provided. In addition, in **Chapter 4,** the functional outcomes in patients with facial dysostosis and severe UAO after treatment in our center will be studied.

Mandibular Distraction Osteogenesis

The next part of this thesis will focus on the surgical management of RS patients, with special emphasis on mandibular distraction osteogenesis (MDO). In **Chapter 5** endoscopic findings in MDO will be studied. In **Chapter 6** the feeding and swallowing function following MDO will be examined.

Discussion, future directions, and summary

Study outcomes, including clinical implications, will be discussed in **Chapter 7**. Furthermore, clinical recommendations will be drawn and future directions will be proposed. In **Chapter 8 & 9**, the most important findings will be summarized in both an English and Dutch summary.

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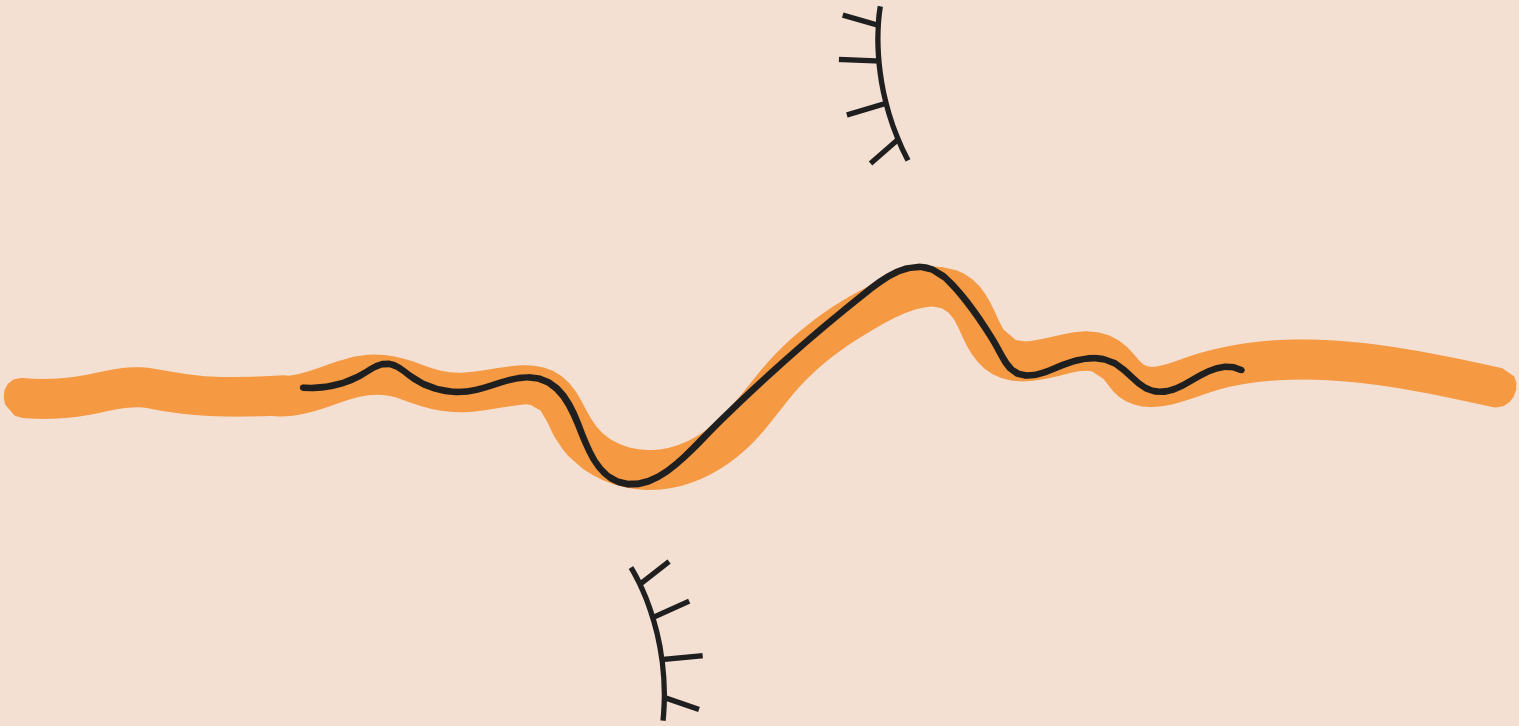

Can the Nasion-Mandibula Ratio Predict Obstructive Sleep Apnea in Patients With Retrognathia?

CHAPTER 2.

Can the Nasion-Mandibula Ratio Predict Obstructive Sleep Apnea in Patients With Retrognathia?

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ABSTRACT

Introduction: Robin Sequence (RS) is characterized by retrognathia, glossoptosis, and upper airway obstruction (UAO). Nonetheless, the exact role of retrognathia in RS remains unclear. The aim of this study was to evaluate if measuring retrognathia could be of use next to the polysomnography (PSG) in the diagnosis of RS by differentiating RS and controls. Furthermore, this study endeavored to evaluate mandibular growth over time.

Methods: A retrospective study was performed on RS patients without life-threatening UAO and controls. Mandibular length was assessed by using the Nasion-Mandibula Ratio (NMRatio) at the following three time points: 0-3 months, 1 year, and 4 years of age.

Results: A total of 107 patients were included, of whom 38 were diagnosed with RS. Thirty-two patients presented with clinical retrognathia but without obstructive sleep apnea (OSA), whilst 37 patients had an isolated cleft palate (CP). At 0-3 months, 1 year, and 4 years of age, significant higher NMRatios were found in RS patients compared to isolated CP patients, whilst no significant differences were found compared to retrognathia-only patients. Within RS patients, no significant differences were found between isolated versus non-isolated and invasively versus non-invasively treated patients. In all 3 patient groups, a significant decrease of the NMRatio was seen at the age of 4 years compared to 0-3 months and 1 year.

Conclusions: Although the NMRatio differs between RS and isolated CP patients, a seemingly small mandible (in a-p direction) does not reflect functional outcomes in RS patients and a PSG should always be performed to confirm the diagnosis. Despite that mandibular length significantly increased after the first year of life, mandibular size of RS patients does not seem to reach values of normal infants. Accordingly, mandibular catch up growth, that is suggested to be typically present in RS patients, was not found by our study.

INTRODUCTION

Robin Sequence (RS) is a craniofacial anomaly, occurring in approximately 1/5600 live births (1). As the word 'sequence' implies, the primary anomaly causes secondary and tertiary problems. In case of RS, retrognathia induces backward placement of the tongue (glossoptosis) which subsequently results in tongue-based upper airway obstruction (UAO). Although it is not a prerequisite of the triad, a cleft palate is present in 80- 90% of the cases (2-4). The characteristic triad of RS can occur in isolation (isolated RS), but may also be present in combination with additional anomalies or syndromes (non-isolated RS), with over 50 associated syndromes described (5, 6).

Severity of UAO in RS patients varies considerably: some patients present with severe and continuous obstruction requiring immediate intervention, whilst in others the respiratory distress occurs intermittent and symptoms are mild and less evident. UAO often aggravates during sleep, especially in supine position due to gravity that forces the tongue to fall backwards, physically obstructing the airway. Obstructive sleep disordered breathing (SDB), characterized by pharyngeal collapsibility and upper airway resistance, is the intermittent dysfunction of the upper airway during sleep and encompasses a spectrum of clinical entities ranging from primary snoring to obstructive sleep apnea (OSA) (7-9). Early diagnosis and treatment are of paramount importance in these children, as untreated OSA may lead to serious comorbidities and in extreme cases sudden death, with mortality rates up to 20% (8-12). So far, various treatment options have been studied (2, 7). Although studies unanimously agree that treatment should start with the least invasive options, management strategies and protocols vary per center (13).

The gold standard to diagnose presence and severity of OSA in both the adult and the pediatric population is a polysomnography (PSG) (14-16), whereas an endoscopy of the upper airway can be used to identify the level(s) of obstruction (17). Defining and objectifying retrognathia, however, is proven to be a challenge. Various methods to assess and quantify mandibular size have been proposed, including the use of lateral cephalogram, CT, MRI, or direct measurements on sight with rulers and calipers. Nonetheless, no method is currently considered as golden standard (18, 19). Although CT and MRI are able to provide a very precise visualization, it is not feasible to perform these diagnostic modalities in all patients with the suspicion of RS due to radiation exposure and high costs. Furthermore, the limited availability and need for positioning and immobilizing the infant restrict (daily) use. Another issue that prevents diagnosis of retrognathia is that normative data on infant mandibles are lacking. Consequently, there is still no widely accepted classification system to characterize retrognathia. Hence, diagnosis of retrognathia is nowadays mostly based on clinical

evaluation on sight and therefore largely subjective (17, 19). Furthermore, it remains unclear whether or not mandibular length is a sensitive and/or specific predictor for the presence of OSA since some patients with a seemingly small mandible do not present with OSA and vice versa. Moreover, it remains unknown how mandibular growth evolves over time (20). Delineating the role of retrognathia can be the first step towards a better understanding of this complex and challenging clinical picture. Therefore, we endeavored to assess mandibular length by developing a new non-invasive, simple and safe method using straight forward digital photography. With this study we aimed to evaluate: 1) the role of mandibular length in diagnosing RS; 2) the reliability and reproducibility of our measuring method to determine mandibular length; and 3) the mandibular growth over time; on a retrospective cohort from our center.

METHODS

In this study, we retrospectively reviewed data and photographs of patients who were treated between 2007 and 2020 in Sophia Children's hospital in Rotterdam, the Netherlands. The study was approved by the by the medical ethical committee of the Erasmus Medical Center (MEC-2017-126). Patients were considered for inclusion if the diagnosis of RS was suspected, based on the presence of clinical symptoms that were reported in the electronic patient files: mandibular hypoplasia, retrognathia or micrognathia, and the suspicion of OSA. Suspicion of OSA was considered if one of the following clinical symptoms were reported: snoring, retractions, use of accessory muscles, stridor, sleepiness, witnessed apnea, blue lips, and saturation drops during feeding. In all patients with the suspicion of OSA who were not directly in need of respiratory support or intervention, a PSG was indicated in our center.

We collected and reported the following data of patients: sex, day of birth, date of when the lateral photograph was taken, presence of a cleft palate, presence of concomitant abnormalities or the presence of a syndrome. In patients who underwent a PSG, date and outcomes of this PSG were reported, scored according to the AASM criteria and the International Pediatric Otolaryngology Group (IPOG) consensus (14, 16). The following parameters were assessed (if available): number of (central and) obstructive apneas and hypopneas, defined as the obstructive apnea hypopnea index (oAHI) and capillary blood gas values, including pH, O2 , HCO3, Base Excess (BE), pCO2, and oxygen desaturation index (ODI). If present, type and duration of respiratory management were reported.

To date, normative data on mandibular length is lacking. In an attempt to compare mandibular length of RS patients with patients who have a mandible that is, as far as we know, normal and of whom relevant data was available in a chronological order, we included patients with an isolated cleft palate (CP) as a control population. These patients were considered eligible for inclusion if: 1) no clinical presence of retrognathia was reported; 2) no clinical signs of respiratory distress (or PSG) were present; 3) no additional syndromes or comorbidities were found. Noteworthy, not all of our patients underwent (the most up-to-date) genetic diagnostic testing. For this reason, some patients can become part of (another) syndromic spectrum in the future.

Patients were included for final analysis if they had a lateral photograph taken in the first 3 months (≤92 days) of life. Exclusion criteria were: 1) infants with respiratory problems caused by other factors than retrognathia; 2) infants who underwent mandibular or midfacial surgery before lateral photographs were taken; 3) photos that could lead to inaccuracy of our measures (e.g. photo where the child had the mouth wide open or if one of the 3 landmarks was not visible); 4) patients with the suspicion of OSA but in whom no clinical PSG was performed; 5) patients presenting with such respiratory insufficiency, requiring immediate respiratory support (e.g. direct intubation or a tracheostomy tube).

Based on clinical symptoms and the outcome of the PSG, patients were stratified into 3 groups:

1) Study group: **RS patients**, defined as the presence of clinical retrognathia and OSA, determined by a PSG
2) Control group 1: **Retrognathia patients**: patients who presented with clinical retrognathia but without OSA, determined by a PSG
3) Control group 2: isolated cleft palate **(CP) patients** without clinical retrognathia or OSA

For all patients included in final analysis, mandibular length was assessed by determining the position of the mandible relatively to the nasion, which was scored according to the Nasion-Mandibula Ratio (NMRatio). Measures of the NMRatio were performed by using the image-processing program "Image J" for Windows **(Figure 1).** The ratio was calculated by executing the following method: first, the distance (in pixels) between the most distant point of the tragus of the ear to one of the following two landmarks was measured: soft tissue nasion (N') and the soft tissue pogonion (P'), respectively distance A (nasion) and B (mandible). Thereafter, the NMRatio was calculated by executing the following formula: distance A divided by distance B, multiplied by 100. Patients who additionally had a lateral photograph at 1 year and/or 4 years of age had to be taken from the same side of the face (left or right).

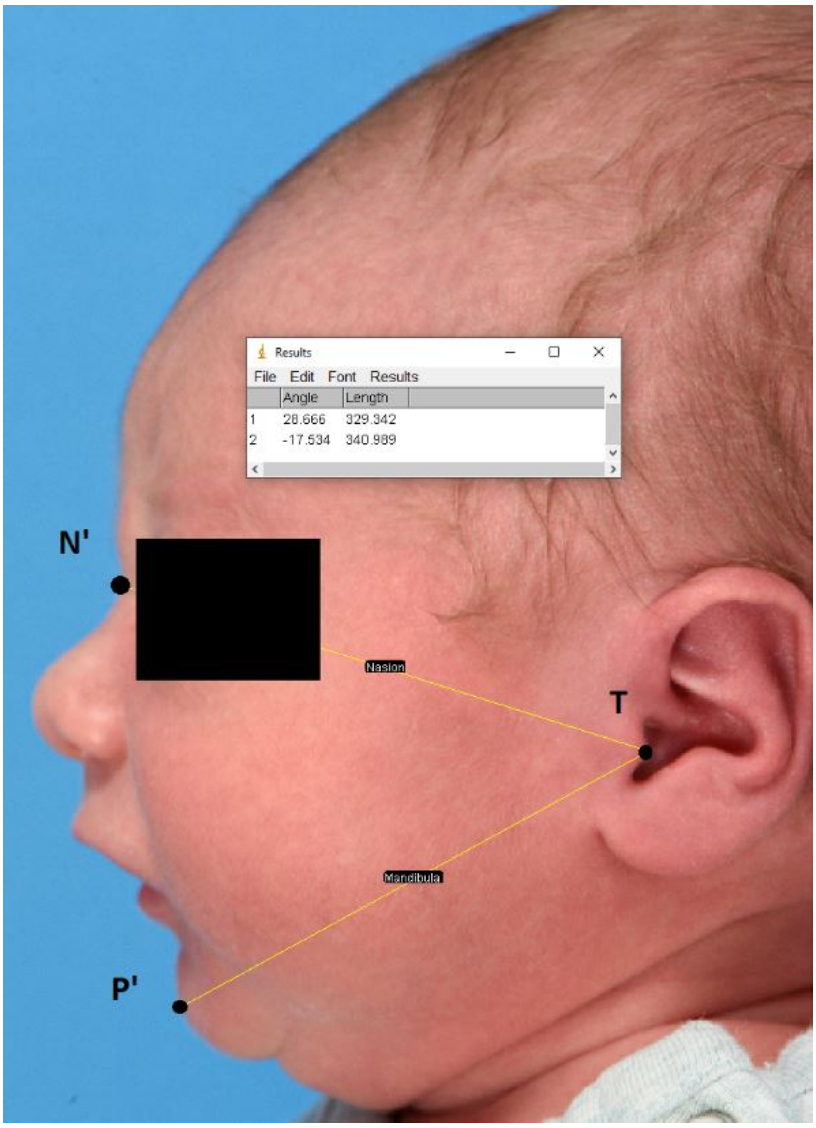

Figure 1. Representation of the Nasion-Mandibula ratio

Definitions of used craniofacial landmarks: ***Tragus (T)*** *= cartilaginous prominence anterior to the meatus acusticus externa.* ***Soft tissue Nasion (N')*** *= the most posterior point of the concavity (soft tissue) between the nose and forehead in midsagittal plane.* ***Soft Tissue Pogonion (P')*** *= most prominent anterior point of the chin (soft tissue) in midsagittal plane.* ***NMRatio*** *= Nasion-Mandibula Ratio: (Nasion (distance A)/Mandibula (distance B)) × 100*

Statistics

To test the reproducibility of our method, inter- and intraobserver variabilities were calculated. The interobserver variability was assessed by using a Two Way Random Model with an absolute agreement scale to calculate the Intraclass Correlation Coefficient (ICC). The intraobserver variability was assessed by using a Two Way Mixed Model with an absolute agreement scale to calculate the ICC. The following cut off values for the ICC were used: values less than 0.5 indicated poor reliability, values from 0.50 – 0.75 indicated moderate reliability, values from 0.75 – 0.90 indicated good reliability and values above 0.90 indicated excellent reliability (21, 22). Bland-Altman plots with 95% limits of agreement were performed to visualize the degree of agreement (23).

To test the differences between groups, an independent samples T-test for continuous normally distributed data, a Mann Whitney U Test for continuous, non-normally distributed data and a Fisher's Exact Test for dichotomous data was executed. To compare mandibular length over time, a paired t-test for normally distributed data or a Wilcoxon singed rank test for non-normally distributed data we performed. SPSS statistics version 25 for Windows (IBM Corp., Armonk, N.Y., USA, 2017). P-values lower than 0.05 were considered as statistically significant.

RESULTS

A total of 159 patients had a lateral photo in the first 3 months of life. Fourteen patients had such an open mouth that it was not representative to score the NMRatio. Twenty-nine patients did not undergo a clinical PSG, whilst another nine patients received a tracheostomy after the first photo and these patients were therefore excluded from further analysis. A total of 107 patients were included in this study of whom 58 patients were male (54.2%). Thirty-one patients presented with additional comorbidities or a syndrome (29.0%). Thirty-eight patients were diagnosed as RS patients as they presented with clinical retrognathia and OSA objectified by a PSG (RS patients). Thirty-two patients presented with clinical retrognathia but without OSA determined by a PSG (retrognathia patients, control group 1). The remaining 37 patients presented with an isolated cleft palate, without clinical retrognathia or (clinical) signs of respiratory distress (isolated CP patients, control group 2). Patient characteristics are presented in **Table 1.**

Table 1. Patient Characteristics

Group	**Robin Sequence**	**Retrognathia**	**Isolated CP**	**Total**
	n=38	**n =32**	**n=37**	**n=107**
Age*, median(IQR)	11.0 (7.9-34.5)	11.5 (8.0-25.3)	10.0 (7.0-14.5)	10.0 (8.0-19.0)
Male sex, n(%)	25 (65.8%)	16 (50.0%)	17 (45.9%)	58 (54.2%)
Cleft palate present, n(%)	34 (89.5%)	30 (93.8%)	37 (100.0%)	101 (94.4%)
Non-isolated, n(%)	17 (44.7%)	14 (43.8%)	0 (0.0%)	31 (29.0%)

***CP** = Cleft palate; **n** = number of patients; **%** = percentage within the particular group*
**At time of first photo*

The median age at time of the first photo was 10.0 (IQR 8.0-19.0) days. Eighty-six patients had a lateral photo at the age of 1 year (median age 286.0 (IQR 273.0-312.3) days), whereas 57 patients had a lateral photo at the age of 4 years (median age 1484.0 (IQR 1462.5 – 1503.0) days). The ICC that assessed interobserver variability for the measured NMRatio was 0.987 (95% CI [0.977-0.993]), which represents excellent agreement. The ICC that assessed intraobserver variability was 0.808 (95% CI [0.655 – 0.894], which represents good agreement. Bland Altman plots for both the intraobserver variability and interobserver variability are represented in **Figure 2**.

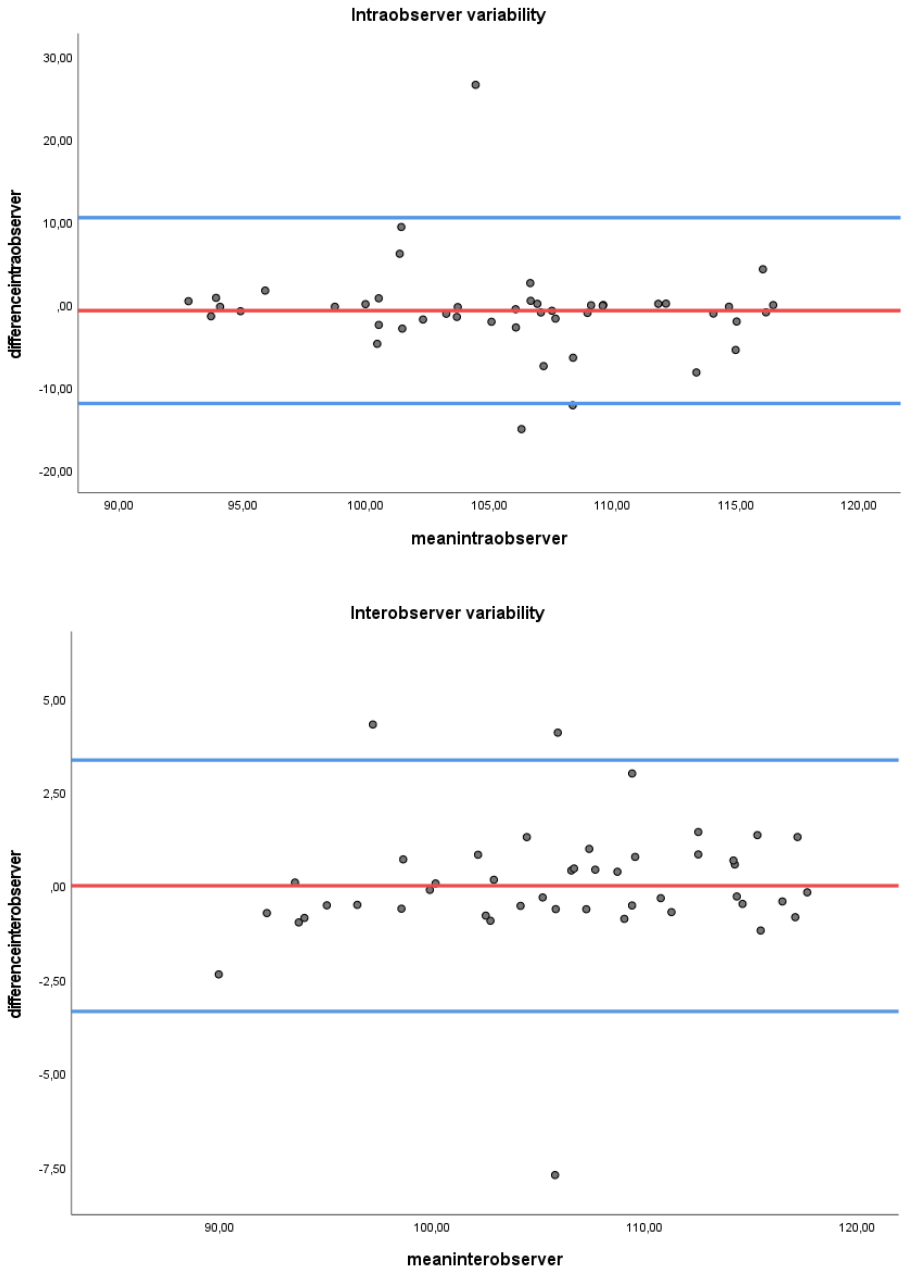

Figure 2. Bland Altman plots of the intra-and interobserver variability

***Bias** = 95% limit of agreement; **Red horizontal line** = mean. **The upper blue line** = the upper 95% limit of agreement at a position of (mean + [standard deviation × 1.96]). **The lower blue line** = the lower 95% limit of agreement at a position of ([standard deviation × 1.96] − mean).*

In all subgroups (e.g. isolated CP, retrognathia, and RS), significant differences were found between the NMRatio at the age of 4 compared to the age of 0-3 months (respectively p=0.001, p=0.005, and p<0.001) and compared to the age of 1 year (respectively p=0.001, p=0.011, and p<0.001). No significant differences in NMRatio were found in all subgroups between the age of 0-3 months and 1 year. The NMRatios at 0-3 months, 1 year, and 4 years of age of all patients are presented in T**able 2.**

Differences between Robin Sequence patients and controls (Table 3)

At the age of 0-3 months, 1 year, and 4 years, a significant higher NMRatio was found for RS patients compared to isolated CP patients, respectively p=0.007; p=0.014; and p=0.045. No significant differences of the NMRatio was found at 0-3 months, 1 year and 4 years between RS patients and retrognathia patients. Between retrognathia and iCP patients a significant difference was found at the age of 0-3 months and 1 year, but not on the age of 4 years, respectively p=0.008, p=0.018, and p=0.162. Differences between RS patients and controls are presented in **Table 3**.

Differences within Robin Sequence patients (Table 4)

Twenty-three out of 38 RS patients were treated with prone positioning, whereas the other 15 patients required more invasive therapies (Continuous Positive Airway Pressure (CPAP), Oxygen (O2), and Nasopharyngeal Airway (NPA)). Seventeen patients were diagnosed with non-isolated RS as they presented with a syndrome or with additional comorbidities, whilst the other 21 patients had isolated RS. At all ages, there were no significant differences in NMRatio of RS patients who were treated with prone positioning versus patients who received more invasive treatment. Furthermore, there were also no significant differences found between the NMRatio of isolated RS patients compared to non-isolated RS patients. Differences within RS patients are presented in **Table 4**.

At all ages, significant differences were found between non-isolated RS and isolated cleft palate patients, respectively p=0.008; p=0.023; and p=0.021. No significant differences were found between isolated RS patients and isolated CP patients. Differences between isolated RS patients and non-isolated RS patients and controls are presented in **Table 4**.

Table 2. NMRatio at different ages

Group / *NMRatio*	Robin Sequence	p-value	Retrognathia	p-value	Isolated CP	p-value	Total	p-value
Age 0-3 months, Median (IQR)	104.9 (100.0 - 112.2)		105.6 (101.4 - 109.5)		101.5 (98.3 - 105.1)		103.5 (100.2-108.4)	
Age 1 year, Median (IQR)	105.7 (100.1 - 109.7)		104.1 (101.5 - 106.9)		99.5 (94.5 - 102.8)		102.8 (98.0-108.7)	
Vs. 0-3 months*,^	105.8 (100.0 - 112.2)	p=0.410	106.5 (101.4 - 109.5)	p=0.263	101.5 (98.2 - 105.5)	p=0.351	103.4 (100.0-108.2)	p=0.098
Age 4 years, Median (IQR)	97.7 (94.3 - 104.2)		97.3 (94.0 - 99.5)		93.6 (91.3 - 97.2)		96.4 (92.3-100.1)	
Vs. 0-3 months**,^	107.1 (101.3 - 114.0)	P=0.001	106.8 (102.4 - 111.7)	p=0.005	102.5 (97.4 - 107.2)	p<0.001	104.7 (100.5-109.3)	p<0.001
Vs. 1 year,^	107.9 (100.6 - 112.5)	P=0.001	104.1 (101.9 - 106.2)	p=0.011	100.4 (97.2 - 109.0)	p<0.001	103.7 (98.7-109.0)	p<0.001

***NMRatio** = Nasion-Mandibula Ratio, **CP** = Cleft palate; **IQR** = Interquartile Range*

**the NMRatio at the age of 1 year compared to the age of 0-3 months*

*** the NMRatio at the age of 4 years compared to the age of 0-3 months*

**** the NMRatio at the age of 4 year compared to the age of 1 year*

*^individual patients were compared (2 related groups), so number of patients was equal in both groups (for example: RS at age 0-3 months: n=38; RS at age 4 years: n=21, so analysis of *** was based on a number of 21 patients).*

Table 3. Differences between Robin Sequence patients and controls

NMRatio	Robin Sequence (RS)	Retrognathia (Re)	Isolated CP (iCP)	RS vs Re p-value	RS vs iCP p-value	Re vs iCP p-value
NMRatio 0-3 months, Median (IQR)	104.9 (100.0 - 112.2)	105.6 (101.4 - 109.5)	101.5 (98.3 - 105.1)	p=0.804	p=0.007	p=0.008
NMRatio at age 1 year, Median (IQR)	105.7 (100.1 - 109.7)	104.1 (101.5 - 106.9)	99.5 (94.5 - 102.8)	p=0.440	p=0.014	p=0.018
NMRatio at age 4 years, Median (IQR)	97.7 (94.3 - 104.2)	97.3 (94.0 - 99.5)	93.6 (91.3 - 97.2)	p=0.512	p=0.045	p=0.162

***NMRatio** = Nasion-Mandibula Ratio ; **CP** = Cleft palate; **IQR** = Interquartile Range*

Table 4. Differences within Robin Sequence patients

NMRatio	Isolated RS (i-RS)	Non-isolated RS (ni-RS)	Isolated CP (iCP)	i-RS vs ni-RS p-value	i-RS vs iCP p-value	Ni-RS vs iCP p-value	Non-invasively treated* RS	Invasively treated** RS	p-value
Age 0-3 months, Median (IQR)	103.5 (100.0 - 109.9)	108.1 (101.2 - 114.2)	101.5 (98.3 - 105.1)	p=0.311	p=0.074	p=0.008	103.7 (100.0-112.2)	105.8 (100.9-113.5)	p=0.601
Age 1 year, Median (IQR)	104.4 (98.2 - 108.8)	108.8 (101.2 - 112.6)	99.5 (94.5 - 102.8)	p=0.266	p=0.088	p=0.023	105.3 (98.4-109.7)	108.6 (102.3-112.6)	p=0.591
Age 4 years, Median (IQR)	97.3 (91.2 - 103.1)	99.4 (95.1 - 106.0)	93.6 (91.3 - 97.2)	p=0.385	p=0.256	p=0.021	97.7 (95.0-101.7)	99.1 (90.7-108.6)	p=0.938

***NMRatio** = Nasion-Mandibula Ratio; **CP** = Cleft palate **IQR** = Interquartile Range*
**non-invasively treated = treated with prone positioning*
*** invasively treated = additional requirement of treatment with Continuous Positive Airway Pressure (CPAP), Oxygen (O2), and/or Nasopharyngeal Airway (NPA)*

DISCUSSION

The results of this study demonstrate that mandibular length as expressed in the Nasion-Mandibula Ratio (NMRatio) is not a sensitive and specific predictor for the presence of obstructive sleep apnea (OSA) in the first 3 months of life in infants with retrognathia. In addition, within the group of Robin Sequence (RS) patients, the NMRatio differed not significantly among those treated non-invasively or invasively, which suggests that a smaller mandibular length, as defined by the NMRatio, is not one-on-one correlated with the severity of OSA. Consequently, mandibular length can solely be used as a guide in the direction of the diagnosis of RS but a polysomnography (PSG) should always be performed to objectify and confirm the presence and severity of OSA.

In this study, no significant differences were found in NMRatio between the retrognathia group and RS group. Since a PSG distinguishes central events from obstructive events, it is able to differentiate RS patients from infants who have respiratory distress caused by other factors than (tongue-based) airway obstruction, including an immature breathing pattern and pulmonary pathology. This underlines that, although RS remains a clinical diagnosis, performing a PSG is crucial for objectifying the diagnosis. Moreover, as a PSG also determines severity of obstruction, it is also very useful in clinical decision making and optimizing individual treatment strategies. Notwithstanding, widely- accepted and standardized cut-off values that consistently guide decision making are currently lacking (13). Probably the most striking part in the diagnosis and treatment of this patient population is that severity of (respiratory) symptoms may vary considerably over time, which makes objectifying RS even more challenging. Therefore, although the results of the PSG are leading, other factors (e.g. clinical signs of respiratory distress, naso-endoscopy) should simultaneously be included in the assessment of these patients. The future possibly brings new diagnostic modalities to assess the (upper) airway that allow more objective measures.

In clinical practice, there are some other non-invasive methods suggested to identify retrognathia that use direct measures with rulers and calipers, such as the jaw-index (JI) or the Maxillary-Mandibular Discrepancy (MMD) (17, 24-26). A recent European survey on practice patterns, however, revealed that only 7% of the responding clinicians used the JI and/or MMD in the diagnosis of RS (27). Although both methods attempted to create a score that is indicative for respiratory distress, both scores were found to have poor sensitivity, which was in agreement with our findings. This further emphasizes that although a seemingly small mandible could make clinicians suspicious for (undetected) airway compromise, mandibular length does not necessarily reflect functional outcomes.

In contrast to the MMD and JI, the NMRatio uses the nasion as reference point instead of the maxilla. Since the maxilla in patients with a cleft palate might be hypoplastic as well due to a disturbed intrinsic growth potential, using the nasion seems to be more accurate (28-33). Furthermore, one of the main benefits of using the NMRatio is that, if the photo is present in the electronic patient file, it can be measured at any moment in time. Lastly, during pediatric development, anatomical structures will rapidly grow and absolute values of mandibular lengths will continuously vary over time. By using a ratio that compares mandibular length to a reference point, the NMRatio mitigates the impact of factors such as age and growth.

The third aim of our study was to evaluate mandibular growth over time. In RS patients, a commonly discussed phenomenon is the so-called mandibular "catch-up growth". This concept hypothesizes that the mandible in RS patients grows relatively faster compared to those of normal infants, resolving the mandibulo- maxillary discrepancy (18). Nonetheless, there is still a lot of controversy in literature about the presence and timing of this mandibular catch-up growth (20). The pathogenesis of retrognathia is suggested to be either deformational or malformational of cause (34). In case of a deformational mandible, the retrognathia occurs secondary to intra-uterine conditions that restrict mandibular growth (34, 35). As soon as the restriction is resolved (after birth), these patients will demonstrate mandibular growth ending up with a (physiologically) normal mandible. In contrast, the theoretical phenomenon of catch-up growth is very unlikely to occur in patients in whom the retrognathia is caused by an inherent growth deficit and these malformed mandibles will still be hypoplastic at end of growth. It is believed that, although it may be present in isolated patients, this inherent defect is pre-dominantly present in non-isolated patients (34-36).

Compared to isolated patients, syndromic patients are believed to have an aberrant mandibular morphology, size, and growth potential (37, 38). Nonetheless, since RS is a very heterogeneous disease, this can also vary considerably among and within different syndromes (37). Our study of patients without life- threatening airway obstruction demonstrated that although the NMRatio was lower (indicating a smaller mandibular length) in non-isolated RS patients compared to isolated RS patients at all ages, these differences were not significant. Noteworthy, however, significant differences were found at all ages between non-isolated RS and isolated CP patients, whilst, despite that the NMRatio was lower in isolated RS patients compared to isolated CP patients, these differences were not statistically different.

These findings indicate that although patients with non-isolated RS are at an increased risk of having a smaller, malformed mandible with disturbed growth potential, the inherent growth deficit is not one-on-one correlated with syndromic status and that some non-isolated patients can have comparable mandibular growth and length to that of isolated patients. We feel that this is an important factor that needs to be taken into account in clinical decision making.

When interpreting our results, one should take into account that the population we have studied did not include those with severe upper airway obstruction, requiring immediate endotracheal intubation or a tracheostomy tube placement. These patients often present with extremely hypoplastic mandibles and severely affected growth potentials and are very unlikely demonstrate mandibular catch up growth (34). Notwithstanding, as these patients require immediate intervention, quantifying the degree of retrognathia is not the primary concern and these patients were therefore not subjected to our study.

In the majority of RS patients, respiratory distress dissolves during the first year of life without the need for surgical intervention (2). Some studies advocate that this natural decrease of severity of obstruction is the result of this presumed compensatory growth of the mandible, which should take place during the first year of life in patients without any form of inherent mandibular growth disturbance (20, 39). In all of our three subgroups, no significant differences were found between the NMRatios at 0-3 months and 1 year of age. Accordingly, the improvement of respiratory distress that occurs during this first year of life could not directly be explained by the presence of this compensating mandibular growth, as expressed by the differences in NMRatio, in this study. Alternative factors that interfere in the respiratory status of RS patients, including the absolute increase of the airway volume (by absolute growth of the neonatal airway and/or a faster mandibular growth relatively to the tongue, resulting in a more anterior tongue position) and resolution of airway collapsibility due to an improved neurological regulation, have already been considered (40, 41). Notwithstanding, it remains unknown what the exact impact of these factors is on airway obstruction and how they evolve over time.

In addition, despite that significant improvement in mandibular length was found within all groups, differences remained present between isolated CP patients and both isolated and non-isolated RS patients. Hence, infants with RS do not seem to catch-up to the same mandibular length compared to the infants with a cleft palate only. This emphasizes that the presence of the so-called catch-up growth, that should be typically present in RS patients, was not identified by our study. We hypothesize that the improvement of NMRatio that occurred in all subgroups is also a result of vertical outgrowth of

the face which seems to occur after the first year of life. Lastly, mandibular length between RS patients and retrognathia patients was similar at all ages, which implies that some infants have a small mandible that will not lead to airway compromise and vice versa. In other words, having a seemingly small mandible does not necessarily mean that the child will have OSA and that it is more a result of phenotypical variation than that it will lead to a pathology. All things considered, our findings underline the etiologically and phenotypically heterogeneity of this disease that will continuously pose challenges to clinicians.

Longitudinal follow-up studies, preferably in a multicenter setting, are needed to further investigate the presence and evolution of mandibular growth in relation with clinical symptoms in this challenging patient population. Elucidating exact underlying pathophysiology of mandibular growth is a crucial step towards a better understanding of these challenging patients and will lay crucial foundation for clinical decision making and optimizing appropriate treatment strategies. Moreover, it may aid to a better organization of follow up, tailored to the specific needs of the individual RS patients.

LIMITATIONS

There are limitations to this study that need to be considered. First, as we took non-invasive lateral photographs, soft tissues were taken into account. Since we did not correct for potential confounders such as ethnicity and body mass index, this may have led to bias in our results. Another limitation of our newly developed method is that we noticed a lot of discrepancies of mandibular positions on the lateral photographs within and between patients. As such, considering it is hard to instruct small children, this could have had an impact on our measurements that we were not able to correct for. For this reason, we excluded photos when the child had such an open mouth to avoid incorrect and misleading outliers. Third, we used a retrospective design which limited the collection of data, such as missing photos or photos with poor quality, incomplete or missing data because of poor reporting. Furthermore, due to the retrospective design of this study, the data is prone to selection bias which may have had an impact on the outcomes. Notwithstanding, we attempted to address this in the best way possible by following our standard management protocol. Last, since there is currently no golden standard to diagnose and objectify retrognathia and normative data on mandibular lengths are lacking, we were not able to compare and validate the outcomes of our newly developed measuring method (yet). Furthermore, although all patients are consulted by the same, experienced, nurse practitioner, diagnosis was largely subjective with a potential risk of inter-and intraobserver variability.

CONCLUSIONS

In summary, this study showed that the NMRatio is a simple, non-invasive, and reproducible method to assess mandibular length during infancy. A small NMRatio, and thus a seemingly small mandible, is not a sensitive and specific predictor for the presence of obstructive sleep apnea in patients with retrognathia and does not allow for any conclusions regarding clinical outcomes. A polysomnography should therefore always be performed to confirm diagnosis. In all groups, a significant improvement of mandibular length after the first year of life was noticed. However, mandibular size of RS patients does not seem to reach values of normal infants at the age of 4 years. Hence, mandibular catch-up growth that should be typically present in RS patients, was not found by our study. Elucidating underlying pathology should eventually result in a more personalized and targeted management and will aid in clinical decision making. Longitudinal follow-up studies athat will evaluat mandibular growth trajectories in patients with retrognathia in relation with clinical symptoms are required.

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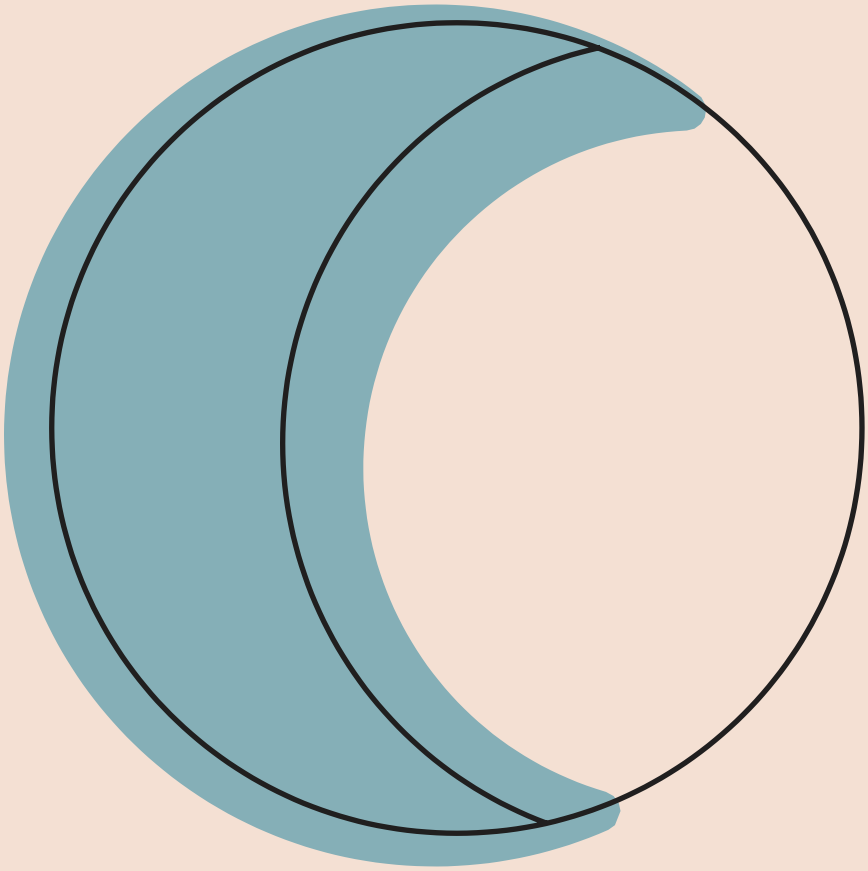

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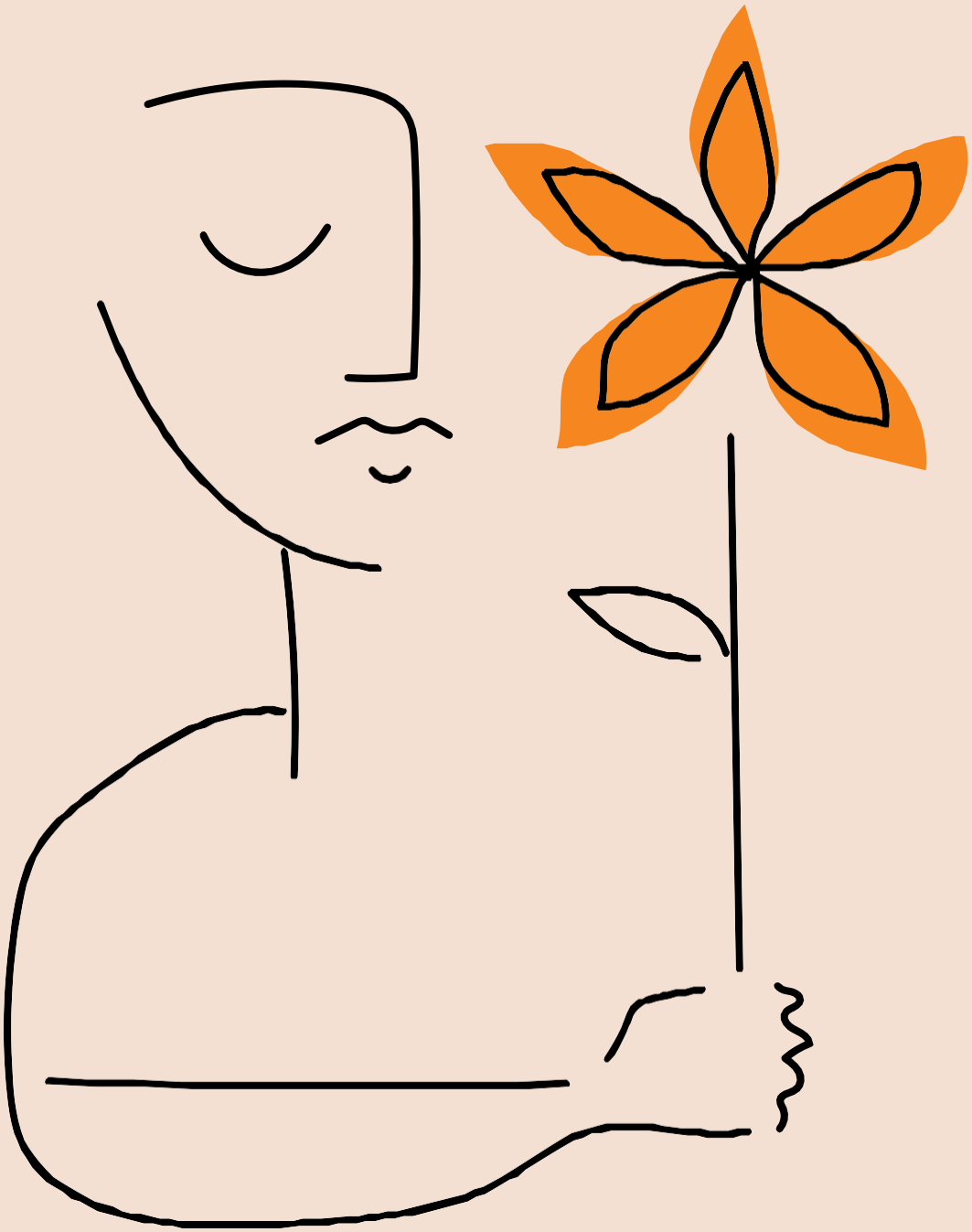

Functional outcomes in patients with facial dysostosis and severe upper airway obstruction

CHAPTER 4.

Functional outcomes in patients with Facial Dysostosis and severe upper airway obstruction

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ABSTRACT

An increased risk of upper airway obstruction (UAO) is seen in up to 95% of patients with facial dysostosis. Secondary to respiratory problems are feeding difficulties and increased nutritional requirements. Little has been described regarding these outcomes in this patient population. Hence, a retrospective cohort study was performed to gather data on functional outcomes. Eighteen patients with facial dysostosis and severe UAO were included. The median follow-up time was 3.42 years. A tracheostomy tube was placed in 13 patients, of whom 10 subsequently underwent mandibular distraction. Three of the five patients without a tracheostomy underwent mandibular distraction as the primary surgical treatment; the remaining two patients were treated conservatively with oxygen supplementation. At presentation, 13 patients had feeding difficulties. Overall malnutrition was present in 16 patients during follow-up. At the end of follow-up, severe UAO was present in 12 patients, feeding difficulties in seven patients, and malnutrition in four patients, while two patients died. In conclusion, patients with facial dysostosis have a high prevalence of severe UAO, feeding difficulties, and malnutrition. Importantly, mandibular distraction has limited success in treating severe UAO in these patients. Close follow-up by a specialized craniofacial team is of paramount importance to manage the long-term consequences.

INTRODUCTION

Facial dysostosis (FaD) is a complex craniofacial abnormality of the skeletal and soft tissues, caused by abnormal development of the first and second pharyngeal arches during embryogenesis (1, 2). FaD can be subdivided into acrofacial dysostoses, which includes Nager syndrome and Miller syndrome, and mandibulofacial dysostoses, which includes Treacher Collins Syndrome (TCS) and Burn-McKeown syndrome (3).

Upper airway obstruction (UAO) occurs in up to 95% of patients with FaD (4). UAO can be caused by multilevel respiratory tract abnormalities and may include deviation of the nasal septum, choanal atresia, and mandibular hypoplasia. UAO may also occur following cleft palate repair (1, 4, 5). In 25% to 41% of patients with FaD the UAO is severe (4). In contrast to what appears to be the case in isolated Robin sequence patients, patients with FaD do not show the tendency of natural improvement over time (5).

Closely related to UAO are feeding difficulties (FD) and swallowing difficulties (SD), as seen in other craniofacial abnormalities with mandibular hypoplasia involvement such as craniofacial microsomia and Robin Sequence (6, 7). The severity of FD and SD appear to be related to the severity of mandibular hypoplasia and UAO (8- 10). Secondary to respiratory problems, FD, and SD is the increased risk for malnutrition and a decline in growth due to inadequate nutritional intake (11). These findings led to the hypothesis that aside from UAO, patients with FaD also have a high risk of developing FD, SD, and malnutrition.

Literature regarding respiratory problems, FD, SD, nutritional status, and long-term outcomes in FaD patients with severe UAO remain limited. Therefore, the aim of this study is to evaluate our experience with the treatment of severe UAO in patients with FaD, regarding respiratory outcomes, feeding and swallowing, and growth.

MATERIALS AND METHODS

A retrospective cohort study was performed on all patients diagnosed with FaD, who were treated by the Dutch Craniofacial Center (Sophia Children's Hospital – Erasmus University Medical Center, Rotterdam) between 2010 and 2019. The study protocol was exempted from review by the institutional research ethics board (MEC-2016-312). Patients were included if they met the following inclusion criteria: 1) genetic or clinical diagnosis of FaD; 2) severe UAO, defined as the presence of a tracheostomy tube or severe OSA clinically confirmed by a polysomnography (PSG) as obstructive-Apnea Hypopnea Index (oAHI) ≥10 (12). Patients who visited the craniofacial center solely for a second opinion, whom did not receive any medical treatment, were excluded from the study. End of follow-up was defined as last clinical visit, death or end of study.

Demographic data

Demographic data were extracted from the electronic patient files: age, date of birth, gender, presence of a cleft palate, and genetic diagnosis.

Respiratory management

Respiratory management in our center was based on the algorithm shown in **Figure 1** (4), which could be customized on the specific needs of the individual patients. Patients with severe UAO were indicated for respiratory support or a tracheostomy tube placement. In patients with tongue-based UAO mandibular distraction osteogenesis (MDO) was considered. MDO was performed from 2 years of age onwards to ensure sufficient bone density for optimal pin retention. In patients with a cleft palate and an indication for palatal closure, a PSG with an orthodontic plate to cover the cleft was performed pre-operatively. In cases of OSA upon the PSG with the palatal plate, the palatal closure was postponed until the PSG was uneventful

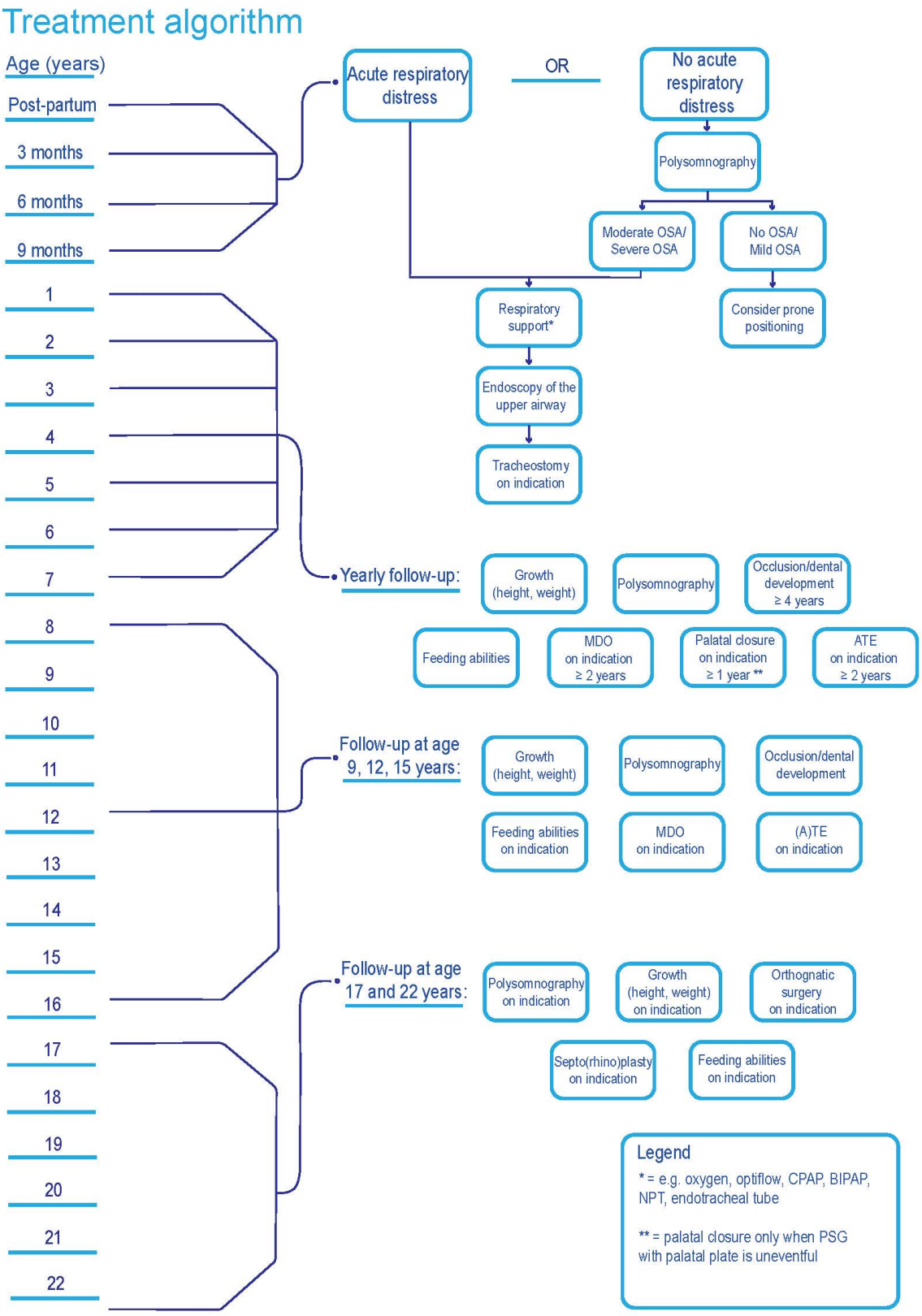

Figure 1. Treatment algorithm for patients with Facial Dysostosis

Treatment algorithm for patients with facial dysostosis with severe upper airway obstruction. Age is provided in years. ***OSA*** *= Obstructive sleep apnea.* ***MDO*** *= Mandibular distraction osteogenesis.* ***ATE*** *= Adenotonsillectomy.* ***A*** *= Adenotomy.* ***TE*** *= Tonsillectomy.* ***CPAP*** *= Continuous positive airway pressure.* ***BIPAP*** *= Bi-level positive airway pressure.* ***NPT*** *= Nasopharyngeal tube.* ***PSG*** *= Polysomnography*

Feeding and swallowing

According to the classification system of Caron et al. (8), FD were classified into three groups (**Table 1)**. Swallowing function was evaluated at the age of 1 to 3 years, as children at the age > 1 year should be able to consume all consistencies, and at latest follow-up. Swallowing function was divided in two phases; the oral phase and pharyngeal phase. This function was assessed during intake of different consistencies (e.g. thin fluid, thick fluid, purees, and solid). Presence of SD was determined if one of the following symptoms was reported during anamnesis or during investigation by speech therapist: powerless sucking, difficulties in chewing, incoordination of sucking, swallowing and breathing, loss of liquid or food from the mouth, exaggerated/excessive choking (gagging), frequent coughing, desaturations, other signs of penetration or aspiration during feeding, nasopharyngeal reflux, and repeated pneumonias.

Table 1. Classification of Feeding Difficulties

Classification	Severity	Description of FD
1	No - Mild	Patient can be fully orally fed, regardless of consistency or feeding mechanism (i.e. Habermann bottle)
2	Moderate	Patient requires additional tube-feeding to acquire adequate intake
3	Severe	Patient is fully dependent on tube feeding

Classification of feeding difficulties according to Caron et al. (8). ***FD*** *= Feeding difficulties.*

Growth and nutritional status

Height and weight were evaluated using growth charts and compared to published standards based on Dutch children and expressed in standard deviation scores (SDS) (13). This resulted in SDS for weight-for-height (WFH), weight-for-age (WFA), and height-for-age (HFA). Overall malnutrition was defined if acute malnutrition and/or chronic malnutrition was present (**Table 2**).

Table 2. Definitions of malnutrition

Type of malnutrition	Criteria
Acute malnutrition	
Age < 1 year old	WFA <-2 SDS
Age 1 - 21 years old	WFH <-2 SDS
Chronic malnutrition	
Age 0 – 21 years old	HFA <-2 SDS
Age < 4 years old	HFA deflection of > 0.5 SDS within 1 year

WFA = weight-for-age. HFA = height-for-age. SDS = standard deviation score based on published standards of the Dutch reference population (13).

Statistical Analysis

The descriptive statistics were reported as percentages in case of count data. Numeric data was illustrated as medians with interquartile ranges (IQR) for non-normally distributed data.

RESULTS

A total of 37 patients with facial dysostosis (FaD) were eligible for inclusion. One patient with severe OSA passed away 10 days post-partum because the parents refused a tracheostomy tube. Consequently, the patient was excluded from further analysis. Eighteen (50%) out of 36 patients presented with severe UAO, including patients with the diagnosis of Treacher Collins Syndrome (TCS, n=13), Nager Syndrome (n=3), Miller Syndrome (n=1), and Burn-McKeown syndrome (n=1). Median age at time of presentation was 0.64 years (IQR 0.01-2.36). Median follow-up time was3.42 years (IQR 1.42-13.74). Patient characteristics are presented in **Table 3**.

Table 3. Baseline patient characteristics

Severe OSA (n=18)			
	Treacher Collins Syndrome n=13	**Nager Syndrome n=3**	**Other* n=2**
Age**(years) (median; IQR)	0.78 (0.1 – 2.4)	0.02 (0.01 – 1.07)	0.79 (0.4 – 1.2)
Sex (n)			
Male	8	2	1
Female	5	1	1
WFH/WFA (SDS) (median; IQR)			
At presentation	-0.7 (-1.3 – 0.5)	-2.2 (-2.6 – -2.0)	-0.9 (-1.2 – -0.5)
Before UAO	-1.4 (-1.8 – -0.8)	-2.6 (-2.8 – -2.6)	
Treatment***			
HFA (SDS) (median; IQR)			
At presentation	-0.8 (-2.6 – -0.3)	-2.8 (-3.1 – -2.0)	-0.7 (-0.8 – -0.6)
Before UAO	-0.4 (-1.4 – 0.1)	-2.7 (-3.0 – -2.3)	
Treatment***			
Cleft Palate (n)			
Solely palatum molle	1	0	0
Palatum molle and durum	7	0	2
Tracheostomy tube (n)	8	3	2
MDO (n)			
Single MDO	7	0	1
Multiple MDO	1	3	1

***IQR** = Interquartile range. **SDS** = standard deviation score based on published standards of the Dutch reference population (13). **MDO** = Mandibular Distraction Osteogenesis. **WFA** = weight-for-age. **WFH** = weight-for-height. **HFA** = height-for- age.*

** Miller syndrome (n = 1), Burn-McKeown syndrome (n = 1).*

*** at time of presentation.*

**** before first UAO treatment in our center. In patients with Burn-McKeown syndrome and Miller syndrome, no weight or height measurement was available prior to UAO treatment.*

Respiratory management

In 13 of the 18 patients a tracheostomy tube (Trach) was placed because of severe upper airway obstruction (**Figure 2**). Ten out of these 13 patients underwent an MDO as subsequent surgical treatment. In the other 3 patients no MDO was performed as they were two years old or younger at time of last follow-up visit. A second MDO procedure was required in three of these ten patients, one patient required three procedures, and another patient required five procedures. Two out of 13 patients additionally received an adenotonsillectomy (ATE) whilst another two patients received a tonsillectomy (TE). At the time of the last follow-up visit, ten patients were still tracheostomy tube-dependent, two patients were decannulated, while one of these ten patients passed away due to chocking 1.7 years after decannulation.

Three of the 18 patients were primarily surgically treated with a MDO. Two out of these patients needed a secondary surgery (TE n=1; Adenoidectomy + TE n=1). UAO reoccurred in all three patients, requiring subsequent non-surgical treatment (CPAP n=2, NPT n=1) 7.9, 6.4, and 1.1 years after MDO treatment respectively. These treatments resulted in elimination of UAO in one patient, persisting UAO in the second patient, while the last patient passed away due to chocking and upper airway infection 10 months after cleft palate repair. In the remaining 2 of the 18 patients overnight oxygen was provided, which led to spontaneous resolution of UAO in one and persisting UAO in the other patient, despite ATE treatment.

Ten (56%) out of 18 patients had a cleft palate, of which nine were repaired. UAO occurred in four out of nine patients following palatal closure. All these patients required immediate respiratory support (NPT n=1, O_2 n=1, Trach n=2) after palatal closure. PSG with orthodontic plate was performed in two patients. Noticeably, no signs of respiratory distress were present pre-operatively on the PSG.

Thus, at the end of follow-up, persisting UAO was present in 12 patients (Trach n=10), elimination of UAO in 4 patients, while 2 patients passed away. UAO resolved initially in nine patients after treatment for severe UAO. In 5 patients, however, UAO reoccurred during follow-up. Median time between MDO procedure and UAO reoccurrence was 6.4 years (IQR: 5.6 – 7.9).

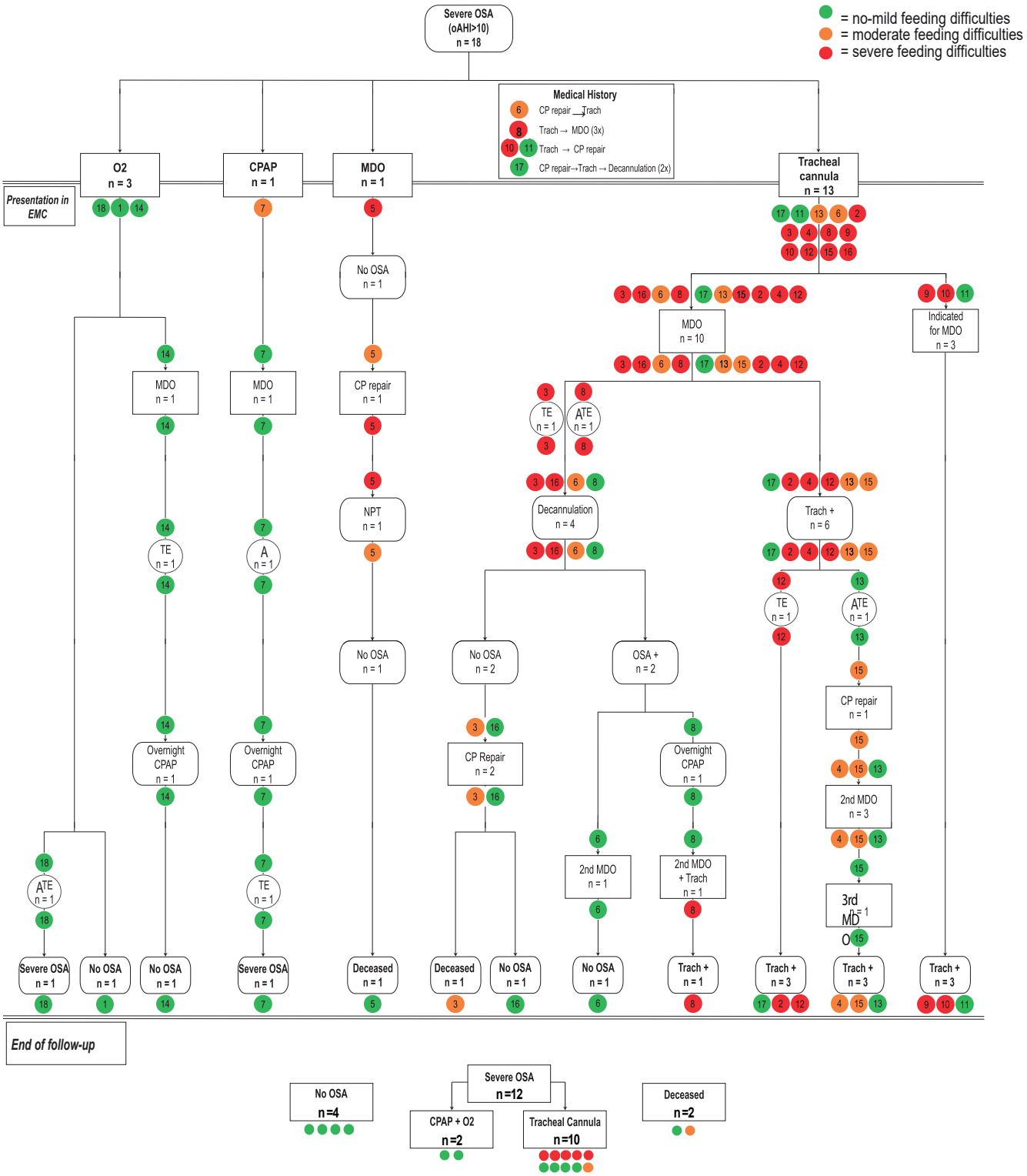

Figure 2. Respiratory management of patients with Facial Dysostosis

Overview of respiratory management in our patient population with FaD and severe upper airway obstruction. ***OSA*** *= Obstructive sleep apnea.* ***Trach*** *= Tracheostomy tube.* ***MDO*** *= Mandibular distraction osteogenesis.* ***CP repair*** *= Cleft Palate repair.* ***CPAP*** *= Continuous positive airway pressure.* ***O2*** *= Oxygen supplementation.* ***NPT*** *= Nasopharyngeal Tube.* ***ATE*** *= Adenotonsillectomy.* ***A*** *= Adenotomy.* ***TE*** *= Tonsillectomy.*

Feeding and swallowing

At the time of initial presentation in our center, five out of 18 patients were fully orally fed and therefore classified as having no-mild FD (**figure 2**). Two of these five patients could eat all consistencies, whereas three patients had problems with chewing and were limited to intake of fluid consistencies. Thirteen out of 18 were classified as moderate (n=3) or severe (n=10) FD. Three of these patients were fed by a nasogastric tube, whilst the other 10 patients required a gastrostomy.

During follow-up, FD improved in eight patients. Seven of these improvements were seen following MDO whilst the eight patient showed improvement prior to MDO. Remarkably, both patients underwent MDO and cleft palate repair. At last follow-up visit, 11 out of 18 patients were able to be fully orally fed, while seven patients still had difficulties with feeding (moderate FD (n=2), severe FD (n=5)). All patients who had persisting FD at end of follow-up were fed by a PEG-tube (n=7).

A form of SD was present in 15 out of 18 patients during the study period. Eight patients had problems solely in their oral phase of swallowing whilst seven patients had problems in both the oral and pharyngeal phase of swallowing. At last follow-up visit, four out of 18 patients did not have any SD. Difficulties in both phases remained in three patients, while eleven patients only had difficulties in their oral phase. Four out of these 11 patients who initially had difficulties in both swallowing phases also showed improvement in their FD during follow-up. Notwithstanding, two patients (mild FD (n=1), moderate FD (n=1)), who showed improvement in the pharyngeal phase of swallowing, passed away due to chocking.

Growth and nutritional status

Overall malnutrition occurred in 16 of 18 patients (89%). Median weight-for-age SDS in patients < 1 year old was -2.0 (IQR: -2.32 – -0.90). Median weight-for-height SDS was -1.05 (IQR: -1.78 – -0.03), while median height- for-age SDS was -1.15 (IQR: -1.86 – -0.58). The individual weight and height of patients of our study population, between the age of 1 to 21 years and divided by sex, are shown in **Figure 3**.

At time of first presentation, malnutrition was present in eight patients, of whom one had acute malnutrition, two had chronic malnutrition, and five had a combined form. During follow-up, eight patients endured at least a period of both acute and chronic malnutrition, two patients suffered from only acute malnutrition, and six patients were solely chronically malnourished. A significant deflection of HFA-SDS was seen in six patients. Twelve of these 16 patients had a tracheostomy tube, whilst 10

patients underwent MDO procedure after malnutrition was measured. At the end of follow-up, WFH-SDS was -0.14 (IQR: -1.60 – 0.55) and HFA-SDS was -1.10 (IQR: -1.33 – -0.56). Four patients were still malnourished, of whom one patient had both types of malnutrition, two were acutely malnourished, and one chronically malnourished.

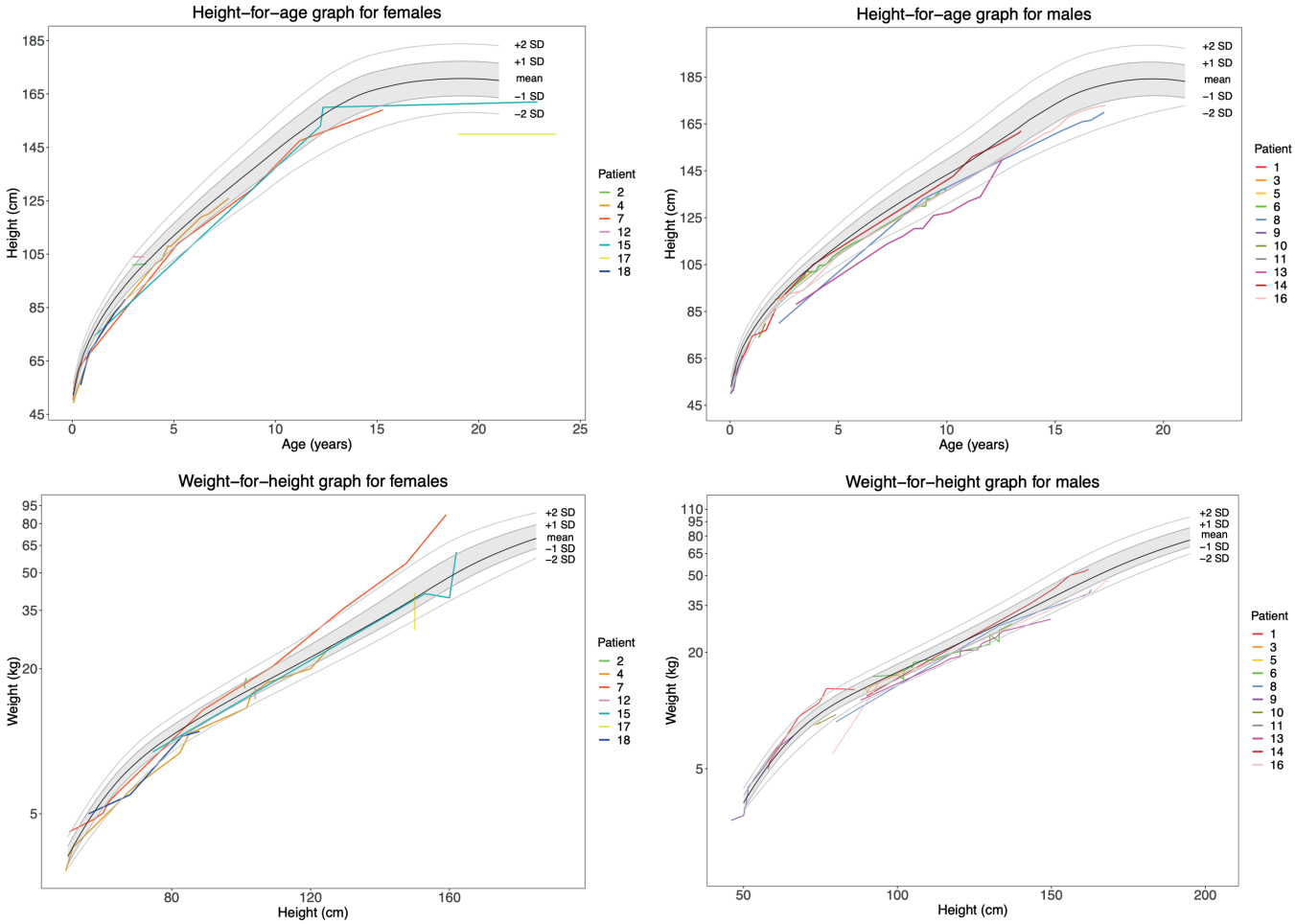

Figure 3. Growth charts of patients with Facial Dysostosis

*Growth of individual patients with facial dysostosis is indicated by colors. Height-for-age graph for female **(A)** and male patients **(B)** are presented, with age in years presented on the X-axis and height in centimeters on the Y-axis. Weight-for- height graph for females **(C)** and males **(D)** are presented using a binary logarithm scale, with height in centimeters on X- axis and weight in kilograms (kg) on Y-axis. Mean measurement of the healthy population is indicated with the middle black line, surrounded by SDS lines.*

DISCUSSION

The aim of this study was to evaluate the effectiveness of treatment of severe UAO in patients with facial dysostosis (FaD), regarding respiratory outcomes, feeding and swallowing, and growth. We have demonstrated a high prevalence (50%) of severe UAO in patients with FaD, which is in agreement with a prevalence up to 41% in previous literature (4). Patients with FaD have a higher prevalence of severe UAO compared to patients with other craniofacial abnormalities, such as isolated Robin sequence (iRS) and craniofacial microsomia (CFM), and matches more the prevalence of severe UAO in Apert and Crouzon syndrome (5, 8, 14). The most striking differences with these syndromic craniosynostosis patients are the less effective treatment of OSA and the common reoccurrence of severe UAO in FaD over time.

In our study, initial MDO had a limited success in treating severe UAO. In one out of three patients without a tracheostomy tube the treatment solved the UAO, while in tracheostomy tube-dependent patients, only four out of ten patients were decannulated (38%). These results are in agreement with a study of 24 patients with FaD in which only 16% of the patients were decannulated within 1 year after MDO (15). Outcomes of MDO in patients with FaD are markedly different compared to the high success rates of decannulation (84%) after MDO in patients with isolated mandibular hypoplasia (16). A systematic review on children with micrognathia showed that the odds of failure after primary MDO in syndromic patients is four times higher compared to isolated patients (16). A repeated MDO failed again in all patients with persistent OSA, illustrating that it is not just a matter of lengthening the mandible. The low success rate of decannulation in patients with FaD might be explained due to obstructions at multiple levels caused by upper airway abnormalities (e.g. choanal atresia), congenital tracheal anomalies, or acquired tube-related complications (5, 16, 17). Another explanation for the low success rate of decannulation following MDO could be due to a neuromuscular collapse of the upper airway which is not corrected with a skeletal correction. The associated swallowing abnormalities appear to be a reflection of a neurological dysregulation (18). The embryological basis for this could be abnormal migration of cranial neural crest cells to the first, second, and fourth pharyngeal arches, which normally give rise to the orofacial structures (1, 2, 19).

Long-term effect of MDO treatment is also a matter of concern, as three out of the five patients with an initial successful treatment developed a reoccurrence of UAO. This percentage is much higher compared to the reported 8% in patients with iRS (15). This could be explained due to the lack of growth on the long-term of mandibles in FaD patients, requiring significantly more consecutive mandibular operations including MDO's than patients with iRS (15, 20, 21).

In our study cleft palate was present in 56% of the patients. Palatal closure gives a considerable risk of reoccurrence or worsening of UAO, as was seen in 4 of our 9 patients. It is important and vastly recommended to first rule out potential UAO by performing a polysomnography (PSG) with orthodontic plate to simulate the closed palate. When UAO is present during PSG, palatal closure should be postponed (4). Our results showed that despite good results of the PSG with an orthodontic plate, severe respiratory distress may still occur.

This study found a high prevalence (72%) of FD at time of presentation. Syndromic patients are found to have a significantly higher risk of FD than patients with isolated mandibular hypoplasia as these patients are five times more likely to require additional tube feeding (22, 23). Additionally, the presence and severity of UAO appear to be correlated with poorer feeding outcomes (8, 24). In our study, improvement in feeding abilities was present in eight of 13 patients with FD. Swallowing difficulties (SD) were present in 15 (83%) out of 18 patients during follow-up. Noteworthy, two patients, who showed improvement in pharyngeal phase of swallowing and were able to be orally fed, passed away due to chocking. Given the high prevalence of FD and SD in our patient population, it is of paramount importance to timely screen for and evaluate feeding and swallowing difficulties over time.

Considering these SD in patients with mandibular hypoplasia, there appears to be a disturbed coordination between the oral and pharyngeal phase of swallowing (25). Most children appear to have problems in the oral phase of swallowing, often leading to difficulty in the pharyngeal phase and/or suboptimal motor function of the esophagus, even if feeding disorders are clinically absent (26). It is hypothesized that this might be caused by the dysregulation of the central pattern generators in the caudal brain stem, as sucking, swallowing, and esophageal motor function are assimilated functions of these central pattern generators (18). It is suggested that eliminating the UAO might lead to an improvement in feeding abilities. However, the aforementioned disturbed neurological findings may explain why, as long as there is dysregulation of the swallowing mechanism, resolution of the UAO will not always solve the FD and SD in these patients (22, 23, 26). It remains unknown how this swallowing function evolves over time and if a complete normal swallowing function can be achieved. Notably, a cleft palate might also affect the oral phase of swallowing, as it is more challenging to build up negative intra oral pressure and more difficult to swallow the bolus (27). One also needs to take into account that the presence of a tracheostomy tube may aggravate feeding and SD (28).

Secondary to respiratory difficulties, FD and SD, there is concern about the growth trajectories of children with FaD. A higher risk of inadequate nutritional intake is present in these patients which may lead to acute and chronic malnutrition and poor developmental outcomes (11, 29). In our study the low SDS for weight-for- height and height-for-age (respectively -1.05 and -1.15) indicate a notable delay in growth compared to the healthy pediatric population. Even more worrisome is the prevalence of overall malnutrition in our study (89%). The percentage of malnutrition in our patient population at the end of follow-up decreased to 22%, with a median weight-for-height SDS and height-for-age SDS of respectively -0.14 and -1.10. These results are in accordance to the literature, which show that resolution of UAO may improve weight gain as seen in patients with iRS (10, 30). Future studies should focus on the long-term consequences of malnutrition (e.g. neurological development) in this patient population.

A number of limitations of this study should be addressed. The retrospective design of our study could have led to scarce or missing data. Nowadays, a PSG, Drug-Induced-Sleep-Endoscopy (DISE), and swallow evaluation are routinely performed in these children using standardized outcome measurements. However, the use of these diagnostic tools has not always been part of our protocol, leading to missing data, especially in the older patients. Secondly, length of follow-up was variable between patients in our study. Furthermore, not all patients were primarily treated in our center. The last limitation is our small sample size of 18 patients. Despite this small sample size, this is one of the first studies to report on feeding, swallowing, and growth outcomes in patients with FaD with severe UAO.

CONCLUSIONS

In conclusion, patients with Facial Dysostosis (FaD) and severe UAO have impaired functional outcomes in terms of respiration, feeding, swallowing and growth. FaD has to be considered as a unique entity compared to other mandibular hypoplasia syndromes, requiring a specific long-term follow-up by a specialized multidisciplinary craniofacial team. The main goals of management in these patients is a combination of treatment of respiratory distress, feeding abilities, swallowing function, and ensuring adequate growth and development.

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Mandibular distraction to correct severe non-isolated mandibular hypoplasia: The role of drug-induced sleep endoscopy (DISE) in decision making

CHAPTER 5.

Mandibular distraction to correct severe non-isolated mandibular hypoplasia: the role of Drug-induced Sleep Endoscopy (DISE) in decision making

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ABSTRACT

Objectives: In patients with mandibular hypoplasia, mandibular distraction osteogenesis (MDO) aims to relieve tongue-based airway obstruction. Drug-induced sleep endoscopy (DISE) provides a dynamic assessment of the upper airway and visualizes anatomical site and cause of airway obstruction. The aim of this study was to evaluate the effect of MDO on tongue-based airway obstruction found by DISE within a non- isolated patient population with severe upper airway obstruction (UAO). Furthermore, we aimed to assess the additional value of DISE in clinical decision making by correlating DISE findings to functional airway outcomes after MDO.

Methods: Findings on DISE in children who underwent MDO were retrospectively gathered and evaluated. According to DISE findings, severity of tongue-based obstruction was scored using a 4-step classification similar to the one that is used by Bravo et al.. Intubation conditions were scored according to the Cormack-Lehane score (CLS). Pre-and postoperative DISE findings were compared and correlated with functional airway outcomes following MDO.

Results: In 19 out of 28 MDO procedures, both a pre-and postoperative DISE was available. Tongue-based obstruction scores improved in 13 procedures, which correlated to a functional improvement in seven. Postoperative tongue-based obstruction differed significantly between patients with successful MDO and patients treated unsuccessfully (2.00 ((Interquartile range (IQR) 1.00-2.00) vs. 3.00 (IQR 2.00-4.00), p=0.028), whereas this difference was not significant for the CLS (1.00 (IQR 1.00-1.50) vs. 2.00 (IQR 1.00- 4.00), p=0.066). If no improvement of tongue-based obstruction was seen, MDO is very unlikely to be successful on the functional airway.

Conclusions: DISE provides information on the site and nature of airway obstruction and can visualize the effect of MDO on the severity of tongue-based airway obstruction. Therefore, it can be of additional value in understanding the differences in functional airway outcomes after MDO and aids in deciding appropriate and targeted treatment. Hence, standardized use of DISE, in addition to the clinical assessment of mandibular position and a polysomnography, during MDO management is highly recommended.

INTRODUCTION

In patients with mandibular hypoplasia (MH), a posterior displaced tongue-base (glossoptosis) can lead to an upper airway obstruction (UAO), which is defined as Robin Sequence (1). This typical triad of characteristics can occur in isolation but can also be non-isolated when present as part of a syndrome or in combination with several comorbidities (2). Severity of UAO can range from mild obstruction only during sleep (obstructive sleep apnea (OSA)) to continuous and serious obstruction requiring immediate endotracheal intubation or tracheostomy tube (3, 4). When left untreated, OSA may lead to various comorbidities such as failure to thrive, cardiovascular problems, an increased risk of psychological problems, and even sudden death in extreme cases (3-8). Hence, early diagnosis, preferably prenatally, and treatment are of paramount importance in these children (9, 10). The vast majority of patients can be managed conservatively (prone positioning, oxygen, nasopharyngeal airway (NPA), and non-invasive ventilation), which we have shown to be sufficient in approximately 90% of the isolated MH patients in our earlier publication (11). Patients with non-isolated MH, however, often present with more severe obstruction and require surgical treatment to improve UAO and provide a safe airway (12-16).

Over the last three decades, mandibular distraction osteogenesis (MDO) has gained popularity as an effective method in relieving tongue-based obstruction in children with severe MH (17). The mechanism is that by distracting the mandible anteriorly, the entire tongue base is moved anteriorly, improving the tongue-based obstruction (18). However, there is currently no consensus on operative indications, timing, and treatment protocol for MDO (14, 17, 19, 20). Therefore, management of these patients is based upon center preference (14, 15, 21). In our center, MDO is reserved for severely affected cases with persistent severe UAO or those who remain tracheostomy tube-dependent and is usually performed from the age of 2 years onwards (11).

Drug-induced sleep endoscopy (DISE) is a diagnostic technique that provides a dynamic visualization of the upper airway. During this investigation, the upper airway is assessed with a flexible scope while patients are in a pharmacologically-induced sleep-like state (22, 23). As DISE provides valuable information on the anatomical site and nature of the airway obstruction it may also aid in deciding which treatment is appropriate for UAO and is therefore widely recommended in the decision-making process for MDO candidacy (17, 24). Nonetheless, literature on the use and outcome of DISE in patients with non- isolated MH is limited, and a clear correlation between functional outcome and DISE outcome after MDO has not been described in this complex population.

The aim of this study was to evaluate the effect of MDO on the tongue-based airway obstruction in patients with non-isolated MH. Furthermore, we aimed to assess the additional value of DISE in clinical decision making by correlating DISE findings to functional airway outcomes after MDO. We hypothesized that DISE findings correlated strongly with functional outcome and could well predict outcome after MDO.

METHODS

A retrospective chart review was conducted on all children diagnosed with severe UAO related to mandibular hypoplasia who underwent MDO in the Sophia Children's Hospital, the Netherlands between 2005 and 2020. The study was exempted from review by the local institutional Medical Ethical Review Board (MEC-2019- 0396). Patients were included if they met the following inclusion criteria: 1) Severe UAO related to non- isolated mandibular hypoplasia**.** UAO was defined as the presence of a tracheostomy tube or the presence of severe Obstructive Sleep Apnea (OSA) necessitating respiratory support. Severe OSA was defined as an obstructive-Apnea Hypopnea Index (oAHI) ≥10, objectified by a PSG, according to the American Academy of Sleep Medicine (AASM-) and International Pediatric Otolaryngology Group (IPOG) consensus (25, 26); 2) MDO performed in the Erasmus University Medical Center; 3) age < 18 years at time of surgery; 4) DISE performed in order to assess UAO. We have focused on the following two outcome measures: 1) anatomical airway outcomes, found by DISE; and 2) functional airway outcomes, defined by the presence and severity of OSA and/or the presence of a tracheostomy tube after MDO.

Local MDO protocol

From the age of 2 years onwards, children who are tracheostomy tube-dependent or those with persistent severe OSA due to mandibular hypoplasia are considered for MDO using external distractors. A stepwise approach that is used in the decision making process before, during and after MDO is presented in **Figure 1**.

Demographic data:

Electronic patient files were reviewed to obtain information on the following patient variables: gender, date of birth, genetic diagnosis, other abnormalities, and relevant medical history.

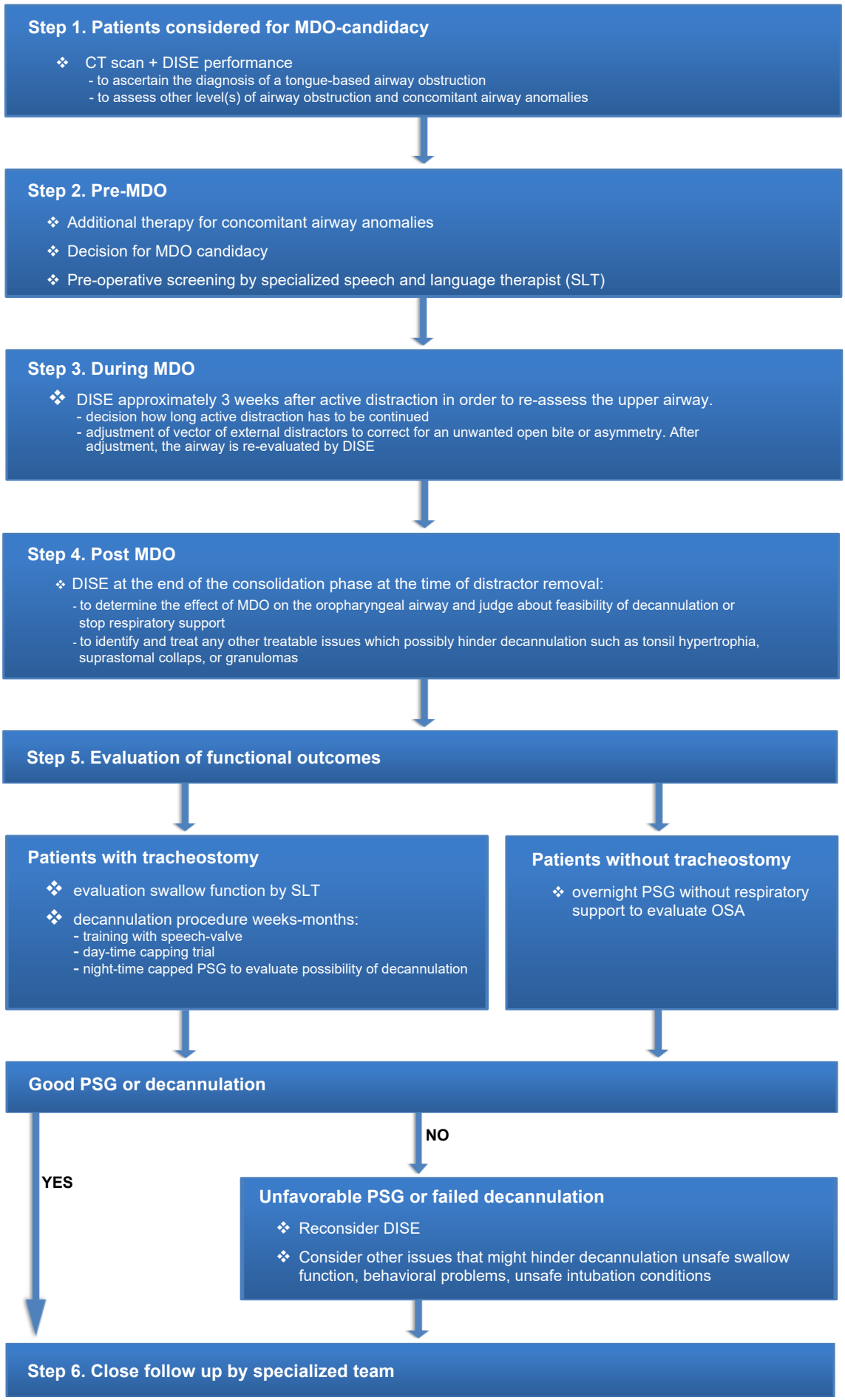

Figure 1. Stepwise approach of MDO protocol
***MDO** = Mandibular Distraction Osteogenesis. **PSG** = polysomnography. **DISE** = Drug Induced Sleep Endoscopy.*

Surgery-specific data and outcomes:

Age at time of initial osteotomy, age at time of distractor removal, and number of distraction procedures were reported. Significant mandibular elongation was defined if the desired mandibular lengthening was achieved (approximately 30-40 mm). In some cases this resulted in an anterior cross bite.

Airway outcomes:

Functional airway outcomes were defined as the presence and severity of UAO, objectified by a clinical PSG or by the presence of a tracheostomy tube. The presence, type, and duration of airway management (e.g. Oxygen (O2), Nasopharyngeal Airway (NPA), Continuous Positive Airway Pressure (CPAP), or tracheostomy tube) were reported. Furthermore, concomitant airway interventions were reported. MDO was considered successful if elimination of UAO was seen and/or if decannulation was achieved and patients were free of UAO after decannulation.

DISE:

Number and timing of DISE procedures were retrieved. Timing of DISE was scored as: pre-MDO which was defined as a DISE directly pre-MDO or within 3 months before MDO, and post-MDO which was defined as a DISE at the end of distraction phase or at time of device removal. Outcome of DISE was retrieved from the theatre records: presence and severity of tongue-based airway obstruction, other anatomical levels of obstruction, and identification of other airway anomalies. The degree of tongue-based obstruction was scored using a 4-step system similar to the one used by Bravo et al. (27). To describe the view obtained by direct laryngoscopy and to assess the likelihood of a difficult orotracheal intubation, the Cormack-Lehane Score (CLS) was used (28). Scores were classified as presented in **Table 1**. Scoring was performed retrospectively by two examiners (BP & PvdP), based on the recorded endoscopy video and/or the endoscopy report. Improvement after MDO was considered if a decrease of at least 1 point in tongue- based obstruction scores was observed on DISE.

Table 1. Classification of DISE-related scores

Classification	Score	Criteria
Tongue-base obstruction score (Bravo et al.)	1	no obstruction, more or less normal endoscopic view with tongue base obstructing less than 25% of the lumen
	2	mild obstruction, with tongue base obstructing 25%-50% of the lumen
	3	moderate obstruction, with tongue base obstructing 50%-75% of the lumen
	4	severe obstruction, with tongue base obstructing more than 75% obstruction of the lumen
Cormack-Lehane Score (CLS)	1	No obstruction
	2	Only posterior glottis seen
	3	Only epiglottis seen
	4	Epiglottis nog visible

Tongue-base obstruction score *= severity of tongue-based obstruction, according to Bravo et al. (27)*
CLS *= Cormack-Lehane Score, according to Cormack et al. (28).*

Statistical Analysis

All analyses were performed using excel and SPSS statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA, 2017). Descriptive statistics were reported as means (±SD) for normally distributed data or as medians (interquartile range (IQR)) for non-normally distributed data. To compare pre-and postoperative outcomes, a paired T-test for normally distributed data or a Wilcoxon signed rank test, for non-normally distributed data was performed. A Mc Nemar's test was performed to examine categorical paired data. To compare two subgroups, an independent T-test for normally distributed data or a Mann Withney U- test for non-normally distributed data was performed. To examine categorical data between two subgroups, a chi- squared test or Fisher's exact test was performed. A p-value <0.05 was considered as statistically significant.

RESULTS

Patient characteristics

A total of 22 patients, consisting of 10 males, underwent MDO in our center. All patients underwent bilateral MDO, except for one patient, presenting with unilateral craniofacial microsomia (CFM). The records of 11 patients were clinically or genetically confirmed by a clinical geneticist (MvD), including: Treacher Collins syndrome (n=6), Nager syndrome (n=3), 22q11 deletion syndrome (n=1), and Trisomy 9 (n=1). In the other 11 patients (bilateral CFM (n=4), unilateral CFM (n=4), syngnathia (n=2), and bilateral cleft lip and palate (n=1)), no syndromic diagnosis was found (yet). However, these patients were also defined as non-isolated MH since these patients presented with additional abnormalities, including skeletal deformities (scoliosis, hip dysplasia), epibulbar dermoid, microtia, pre-auricular skin tags, and macrosomia. Noteworthy, not all of our patients underwent the most up-to-date genetic diagnostic testing. One should bear in mind that, when updating the diagnostic modalities and tests in future, some patients or diseases can become part of another syndromic spectrum or a different category. Nine (40.9%) patients had a cleft palate. Three patients previously underwent an MDO in another center, whereas two patients had a tracheostomy tube in their medical history but were decannulated before referral to our center. Nonetheless, UAO persisted or reoccurred and these patients were therefore indicated for MDO in our center. As six patients underwent a second MDO procedure in our center for persistent or recurrent UAO, we evaluated a total of 28 MDO procedures. Demographic data are represented in **Table 2**.

Table 2. Patient Characteristics

	Total n=22
Male sex, n (%)	10 (45.5)
Cleft palate present, n (%)	9 (40.9)
Airway support pre-MDO, n (%)	22 (100.0)
CPAP	3
CPAP + O2	1
NPA + O2	1
O2	1
Tracheostomy tube*	16
Age (y) at 1st MDO, median (IQR)	3.1 (2.3 - 6.0)
Duration (y) of follow-up after MDO, median (IQR)	3.5 (2.0 - 9.4)
Number of 2nd MDO, n (%)	6 (27.3)
Age (y) at 2nd MDO, median (IQR)	7.8 (7.0 - 11.1)
Decannulated**, n (%)	5 (31.3)
Age (y) at time of decannulation, median (IQR)	3.6 (2.6 - 4.5)
Time (y) to decannulation, median (IQR)	0.8 (0.4 - 1.8)

Age and duration of follow-up are presented in years. ***n*** *= number of patients.* ***IQR*** *= interquartile range.*
MH *= Mandibular hypoplasia.* ***Pre-MDO*** *=Prior to MDO.* ***Post-MDO*** *= At the end of MDO*
** Tracheostomy tube-dependent, including TCS (n=5), Nager Syndrome (n=3), 22q11 deletion syndrome (n=1), Trisomy 9 (n=1), syngnathia (n=2), bilateral cleft lip and palate (n=1). Bilateral Craniofacial Microsomia (n=3).*
***5/16 (31.3%) patients were decannulated, including TCS (n=3), 22q11 deletion syndrome (n=1), Trisomy 9 (n=1).*

In all 22 patients, tongue-based airway obstruction was found on pre-MDO DISE and these patients were therefore indicated for MDO. Concomitant levels of obstruction of the upper airway were found in 11 patients, which included: choanal atresia, nasal septum deviation, and obstruction due to adenoid/tonsil hypertrophy. In 10 patients, the concomitant airway obstruction warranted additional upper airway surgery other than MDO, including: adenoidectomy, tonsillectomy, lingual tonsillectomy coblation, and adenotonsillectomy. The two patients with choanal atresia and nasal septum deviation, however, were still awaiting for repair at time of follow-up. In seven patients, one or more concurrent anomalies of the larynx and trachea were present and included: laryngotracheal stenosis, suprastomal granuloma, and laryngomalacia.

In six of the seven patients, concurrent anomalies of the larynx and trachea were corrected during follow-up, including supraglottoplasty, single stage + double stage laryngotracheal reconstruction (SS-LTR + DS-LTR), and/or microlaryngeal surgery (MLS). One patient was waiting for corrective surgery of the tracheal stenosis at time of follow-up. Concomitant levels of obstructions, airway anomalies, and concomitant airway interventions are represented in **Table 3**.

Table 3. Levels of obstruction

Main level of obstruction	Tongue-base; n= 28
Concomitant levels of upper airway obstruction	Choanal atresia; n=1 Nasal septum deviation; n=1 Adenoid/Tonsil hypertrophy; n=10
Concurrent airway anomalies	Laryngotracheal stenosis; n=3 Granuloma; n=6 Laryngomalacia; n=1
Additional airway interventions	Adenoidectomy; n=1 Tonsillectomy; n=5 Lingual tonsillectomy coblation; n=1 Adenotonsillectomy; n=3 Supraglottosplasty; n=1 SS-LTR + DS-LTR; n=1 MLS; n= 6

***n** = number of MDO procedures**. SS-LTR** = Single Stage Laryngotracheal reconstruction.*
***DS-LTR** = Double Stage Laryngotracheal reconstruction**. MLS** = microlaryngeal surgery.*

DISE findings: pre-MDO vs. post-MDO

In 17 patients, both a pre- and post-MDO DISE was available for comparison and these were included for further analysis. In two out of these 17 patients, a second MDO procedure was performed in our center and included in our analysis. Reasons for second MDO were: no improvement of tongue-based obstruction on DISE after first MDO (Bravo 4-Bravo 4) (n=1) and relapse of tongue-based obstruction during follow-up after MDO (Bravo 2-Bravo 4) (n=1).

Prior to all 19 procedures, severe tongue-based airway obstruction was found by DISE (median tongue-based obstruction score 4.00 (IQR 3.00-4.00)). Tongue-based obstruction scores improved after 13 MDO procedures, whereas after six MDO's, no change was seen. Pre- and postoperative tongue-based obstruction scores differed statistically significant (respectively 4.00 (IQR 3.00-4.00) and 2.00 (IQR 2.00-3.00), p=0.001). Median postoperative tongue-based obstruction score was 2.00 (IQR 2.00-3.00). In 12 MDO procedures, performed in 11 patients, both a pre-MDO and post-MDO Cormack-Lehane score (CLS) was available in the theatre report. Median pre-operative CLS score was 4.00 (IQR 3.25-4.00). CLS improved after 10 MDO procedures, whereas after the other two MDO procedures, CLS remained the same. Median postoperative CLS score was 1.50 (IQR 1.00-2.75). Pre- and postoperative CLS scores differed significantly (respectively 4.00 (IQR 3.25-4.00) and 1.50 (IQR 1.00-2.75), p=0.004). Results of both the tongue-based obstruction scores and the CLS pre-MDO vs. post MDO are represented in **Table 4** and **Figures 2 & 3.**

Table 4. Results of DISE and CLS pre vs. post MDO

DISE airway assessment	**Pre-MDO n=19***	**Post-MDO n=19***	**p-value***
Bravo score, median (IQR)	4.00 (3.00-4.00)	2.00 (2.00-3.00)	p=0.001
No obstruction (1)	0 (0.0%)	3 (15.8%)	
Mild obstruction (2)	0 (0.0%)	7 (36.8%)	
Moderate obstruction (3)	5 (26.3%)	5 (26.3%)	
Severe obstruction (4)	14 (73.7%)	4 (21.1%)	
Cormack-Lehane score	**Pre-MDO n=12**	**Post-MDO n=12**	**p-value****
CLS, median (IQR)	4.00 (3.25-4.00)	1.50 (1.00-2.75)	p=0.004
1)	0 (0.0%)	6 (50.0%)	
2)	0 (0.0%)	3 (25.0%)	
3)	3 (25.0%)	1 (8.3%)	
4)	9 (75.0%)	2 (16.7%)	

***n** = number of DISE procedures. **Pre-MDO** =Prior to MDO. **Post-MDO** = At the end of MDO.*
***Bravo score** = Bravo et al. tongue base score (27). **CLS** = Cormack-Lehane Score (28).*
***= based on the 19 procedures, in 17 patients, with both pre- and post-operative scores, including: Treacher Collins syndrome (n=5), Nager syndrome (n=3), 22q11 deletion syndrome (n=1), Trisomy 9 (n=1), bilateral CFM (n=3), unilateral CFM (n=3), and bilateral cleft lip and palate (n=1).*
***= based on 12 procedures*

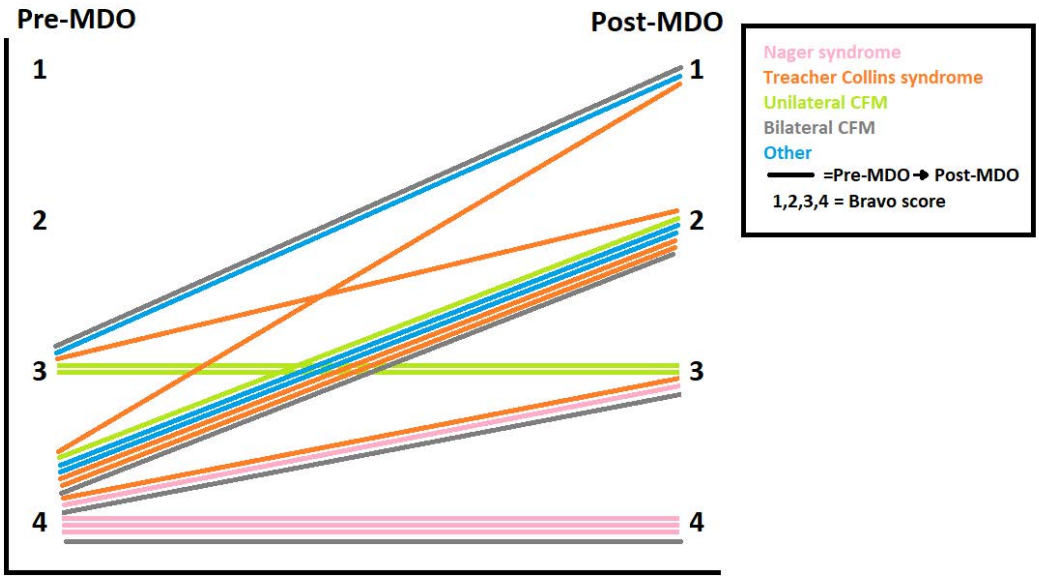

Figure 2. Endoscopic Tongue-based obstruction score outcomes
MDO *= Mandibular Distraction Osteogenesis.* ***Pre-MDO*** *= Prior to MDO.* ***Post-MDO*** *= At the end of MDO.* ***CFM*** *= Craniofacial Microsomia.* ***Other*** *= Syngnathia (n=2), Trisomy 9 (n=1), 22q11 deletion syndrome (n=1), bilateral cleft lip and palate (n=1).* ***Bravo score*** *= Bravo et al. tongue base score (27).*

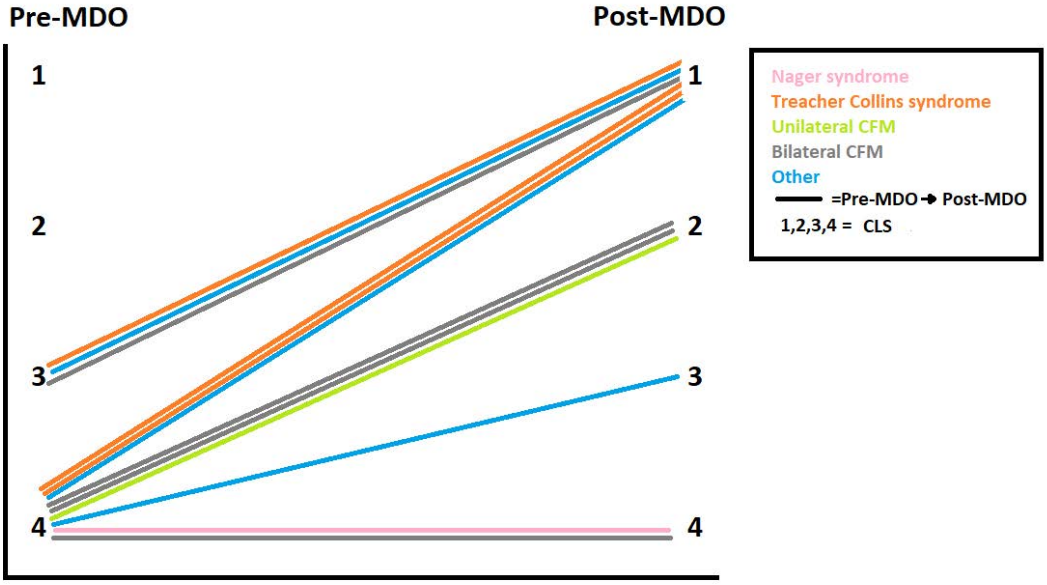

Figure 3. Endoscopic CLS outcomes
MDO *= Mandibular Distraction Osteogenesis.* ***Pre-MDO*** *=Prior to MDO.* ***Post-MDO*** *= At the end of MDO.* ***CFM*** *= Craniofacial Microsomia.* ***Other*** *= Syngnathia (n=2), Trisomy 9 (n=1), 22q11 deletion syndrome (n=1), bilateral cleft lip and palate (n=1).* ***CLS*** *= Cormack-Lehane Score (28).*

Functional outcomes

In seven of the 19 procedures, MDO was successful on the airway; 5 patients were decannulated and in another two patients, without a tracheostomy tube prior to MDO, UAO resolved. In 12 procedures MDO was unsuccessful; after 10 procedures in 8 patients, tracheostomy tube remained present whereas after two MDO procedures, both patients still had moderate OSA after MDO, requiring CPAP.

Correlations between DISE findings and functional outcome

There was a significant difference between postoperative tongue-based obstruction scores of patients with successful MDO compared to patients treated unsuccessfully (2.00 (IQR 1.00-2.00) vs. 3.00 (2.00-4.00), p=0.028). Although postoperative CLS differed between patients with and without successful MDO, this difference was not significant (1.00 (1.00-1.50) vs. 2.00 (1.00-4.00), p=0.066). While tongue-based obstruction scores on DISE improved in 13 procedures after MDO, functional improvement was only seen after seven procedures. The six procedures without functional improvement failed to be decannulated at time of follow- up for a variety of reasons: severe aspiration after MDO (n=3), unsafe intubation conditions (CLS score = 4, n=1), or inability for day-time capping of the cannula which is thought to be behavioral (n=2 procedures, one patient). In six procedures, no improvement in tongue-based obstruction was seen on DISE despite significant elongation of the mandible by MDO. In all six procedures, no functional improvement was seen. If an improvement in tongue-based obstruction was seen on DISE after MDO, the positive predictive value for a functional improvement after MDO is 7/13=0.54 for tongue-based obstruction score and 5/10=0.50 for the CLS score. Endoscopic airway outcomes related to functional outcomes are presented in **Table 5.**

Table 5. Endoscopic airway outcomes related to functional outcomes

DISE airway assessment	All	Successful MDO	Unsuccessful MDO	p-value
Bravo score	**n=19**	**n=7**	**n=12**	
Pre MDO, median (IQR)	4.00 (3.00-4.00)	4.00 (3.00-4.00)	4.00 (3.25-4.00)	p=0.868
Post MDO, median (IQR)	4.00 (3.00-4.00)	4.00 (3.00-4.00)	4.00 (3.25-4.00)	p=0.868
Improvement	13 (68.4%)	7	6	p=0.044
No change	6 (31.6%)	0	6	
Worsening	0 (0%)	0	0	
CLS	**n=12**	**n=5**	**n=7**	
Pre MDO, median (IQR)	4.00 (3.25-4.00)	4.00 (3.00-4.00)	4.00 (4.00-4.00)	p=0.332
Post MDO, median (IQR)	1.50 (1.00-2.75)	1.00 (1.00-1.50)	2.00 (1.00-4.00)	p=0.066
Improvement	10 (83.3%)	5	5	p=0.470
No change	2 (16.7%)	0	2	
Worsening	0 (0%)	0	0	

Pre-MDO *=Prior to MDO.* ***Post-MDO*** *= At the end of MDO.* ***n*** *= number of DISE procedures.*
Improvement *= improvement in DISE-related score of at least 1 point.*
Bravo score *= Bravo et al. tongue base score (27).* ***CLS*** *= Cormack-Lehane Score (28)*

DISCUSSION

This study is one of the first studies that focused on endoscopic airway outcomes found by DISE in a severely affected non-isolated pediatric patient population who underwent MDO. After MDO, a significant improvement of tongue-based obstruction scores was found on DISE, which indicates the effect of mandibular elongation on improving anatomical tongue-based obstruction. Improvement of tongue- based obstruction on DISE, however, does not necessarily imply an improvement in functional outcome since in just 54% of procedures an improvement on DISE outcomes correlated with an improvement in clinical outcome. This underlines the challenge that non-isolated MH patients pose to clinicians as they often present with complex or multiple comorbidities (e.g. swallow dysfunction, unsafe intubation conditions, multilevel obstruction) that may interfere with outcomes. We feel this should be taken into account when treating this complex patient population.

In the pre-MDO setting, DISE confirms the tongue-based obstruction that is correlated to MH. Furthermore, DISE is also important in identifying concomitant airway deficits that can influence further necessary treatment. This study found that almost half of our patients required airway intervention other than MDO, which highlights the complexity of multilevel obstruction in these non-isolated patients. It is our protocol to perform a DISE after approximately 3 weeks following start of distraction. The reason for this is twofold: one is to assess the effect of MDO on the tongue-based obstruction; a decision is made whether or not to continue with active distraction and at what length of distraction to stop. The second reason is that it gives us the opportunity to adjust the external distractors to correct for any asymmetry or unwanted open bite under DISE guidance. In addition, the effect of the adjusted distractors on the tongue-based collapse is also directly evaluated by DISE.

In our institution, a DISE during removal of the distraction device is standard of care to assess improvement of tongue-based obstruction. While a polysomnography (PSG) is essential in objectifying the effect of MDO on functional airway outcome, it does not provide further anatomical information on the level and cause of UAO. As DISE provides dynamic insight into the anatomical airway, it can be of additional value in understanding the differences in functional airway outcomes after MDO. If no improvement on DISE is seen, functional success is very unlikely and performance of a clinical PSG should be reconsidered. Moreover, when there are no safe intubation conditions, we would advise against decannulation despite reasonable results on PSG. In our series, two patients with unfavorable DISE (n=1) and unsafe intubation conditions (n=1) were decannulated after an adequate capped PSG but had to be recannulated quickly afterwards.

When improvement of tongue-based obstruction is seen and decannulation seems feasible, DISE is also used to identify any other treatable issues that possibly hinder decannulation such as tonsil hypertrophy, suprastomal collapse, or granulomas, since multilevel obstruction often occurs in these patients. Hence, DISE performance after MDO, in addition to the clinical assessment of mandibular position and a PSG, might contribute to more targeted treatment and can be helpful in further clinical decision making. Taking these matters into account, we feel that DISE during removal of the distraction device gives valuable information for further treatment of these patients. Although beyond the scope of this study, long-term outcomes are also a matter of concern in these complex, non-isolated patients. Hence, we would highly recommend to perform a DISE during follow-up.

Another standardized part of our airway evaluation is the assessment of the Cormack-Lehane score. Considering that a safely accessible airway is an important condition for decannulation, we feel this is a critical dimension in airway assessment, especially in tracheostomized children. If the CLS is still 4 after MDO, we would not proceed to decannulation and a second MDO may be required.

A surprise finding was that in a number of patients no improvement of tongue-based obstruction was seen on post-MDO DISE, despite the distraction achieving significant elongation of the mandible. It seems that the mechanism of lengthening the mandible to relieve tongue-based obstruction does not apply for all patients with non-isolated MH, especially in patients with Nager syndrome. In all of the latter we found no or very little improvement of tongue-based obstruction, despite mandibular lengthening. Furthermore, two patients remained at a CLS score of 4 despite mandibular lengthening, even after a second attempt in one of the latter. The exact reason why MDO does not improve the airway in these patients remains unknown and will be subject to further research.

Our functional outcomes represent the fact that in our center the MDO procedure is only performed in cases of extremely severe UAO that persists beyond infancy (>2 years). Hence, our study population solely consisted of non-isolated patients, which impacts our success rate. We found that MDO was effective in creating a sufficient airway in terms of elimination of UAO or decannulation in seven (36.8%) of our patients.

Previous studies have reported more favorable respiratory outcomes after MDO compared to our results, with success rates up to 97.6% in isolated patients (17, 29). The presence of a syndrome seems to be a significant predictive factor for severe respiratory distress. For MDO specifically, syndromic patients are at a 4 times higher risk of inadequate airway after primary MDO compared to isolated

patients (17). This is deemed to be caused by the difference in mandibular morphology, mandibular size, and its surrounding soft tissues (30, 31). Moreover, syndromic status also seems to be associated with neurological dysregulation, which in turn might influence respiratory, but also feeding and swallowing mechanisms (32-34). Consequently, treatment of syndromic patients is deemed to be more challenging, resulting in lower success rates, which was also our experience. It would be interesting to compare our results, preferably in a longitudinal, multi-center study, to the outcomes of a cohort of infants with similar diagnoses (non-isolated MH) in whom MDO has been performed during the neonatal period.

Predicting functional outcome of MDO remains challenging. In this study, we were not able to find pre- operative (DISE) characteristics that predict the inability to improve anatomical airway despite mandibular lengthening. Neither were we able to find significant differences between patient groups. However, the finding that the three children with Nager syndrome hardly showed any improvement of tongue-based obstruction during MDO do stand out and has caused us to reconsider the MDO procedure in these patients. We feel clinicians should be wary when consulting parents and patients on the possibilities and limitations of MDO in these severely affected, non-isolated patients. Future studies should focus on elucidating the exact underlying pathophysiology and should aim to identify (patient) characteristics that are associated with poor outcomes.

Limitations

Although this was one of the first studies reporting on endoscopic airway outcomes after MDO, we also acknowledge the limitations. First, our study population consisted of a heterogeneous cohort, all with a variable expression per syndrome. Although we did find that patients with some syndromes seem to do worse than those with other syndromes, we could not draw definite conclusions yet due to heterogeneity of our cohort and the small numbers. Second, the retrospective design of our study is a limitation. Information on pre- and post-operative DISE and amount of mm that was distracted was not always present in our electronic patient file, giving missing data. Moreover, many tongue-base obstruction scores needed to be scored retrospectively from endoscopy recordings and/or the endoscopy report, which could have diminished the validity of our results. Third, in the evaluation of DISE findings, several scoring systems have been developed and validated (35). However, one of the major problems with any endoscopic grading system is the level of variability, limiting accuracy and reproducibility. In this study, we limited ourselves to scoring the tongue- based obstruction using a 4 point scale, similar to that of the classification system of Bravo et al.. Additionally, in case of DISE, the

method of anesthesia/ sedation used and depth of sedation during the investigation will also influence the endoscopic findings. Hence, although DISE allows an objective visualization of the anatomical airway, assessing and grading the severity of obstruction is still subjected to observer interpretation, which could have led to a diminished accuracy and reproducibility of our findings carrying a risk of bias. As long as no method to perform exact volumetric airway measurements is available, interpretation of endoscopy always carries a risk of bias. Hence, this should be taken into account in the assessment and interpretation of DISE findings.

CONCLUSIONS

DISE is a useful tool to identify tongue-based airway obstruction in patients with MH and identify concomitant airway anomalies pre-MDO. After MDO it has merit in assessing the effect of MDO on improvement of tongue- based obstruction and selecting patients for decannulation. This study found that MDO was not always effective in improving tongue-based obstruction, despite adequate bony elongation of the mandible. When DISE results are poor, a functional improvement cannot be expected. However, favorable DISE results do not automatically imply favorable functional outcome or decannulation and other assessments such as swallowing function, identifying multilevel obstruction, safety of intubation, and PSG are still necessary. Nonetheless, DISE is of additional value as “piece of the puzzle”, in understanding the differences in functional airway outcomes after MDO aiding clinicians in dealing with these complex and challenging patients. Hence, we recommend the standardized use of DISE in MDO candidates at pre- and post-MDO time points and advocate the development of a widely accepted, valid, and reproducible classification system. Future studies should focus on identifying DISE findings that are associated with poor outcomes.

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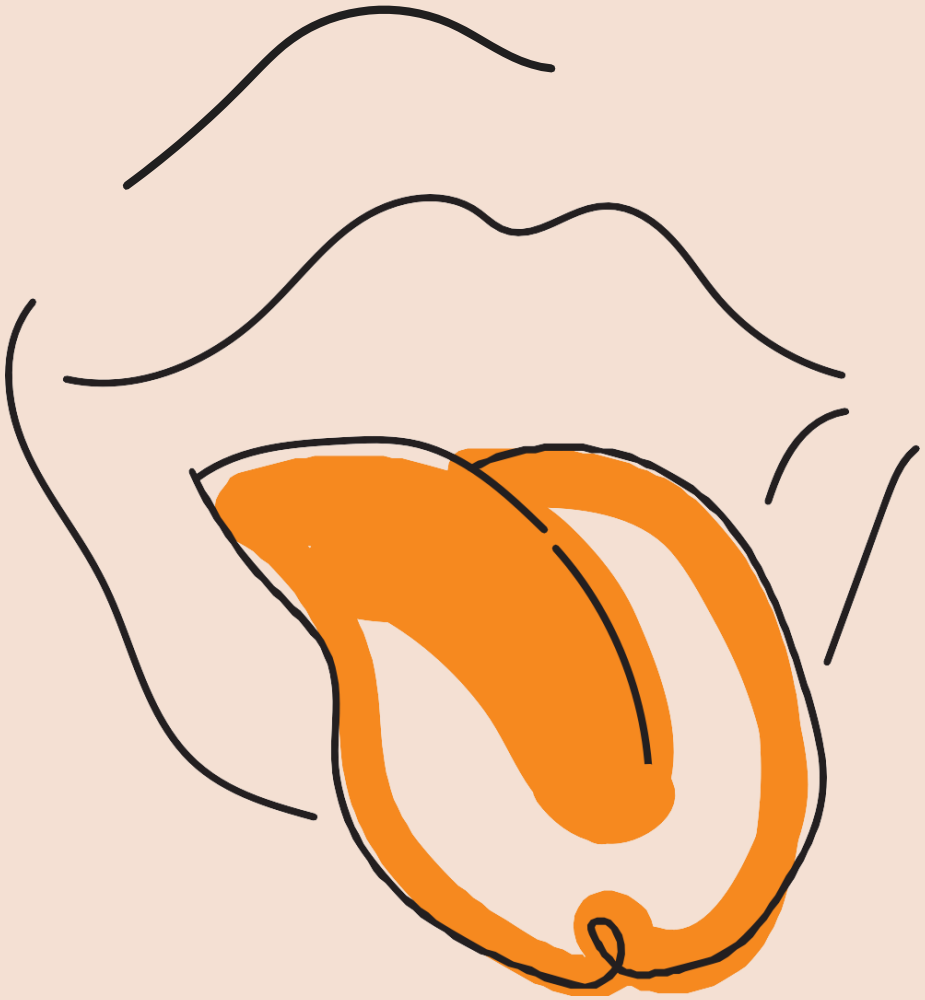

Feeding and swallowing outcomes following mandibular distraction osteogenesis: an analysis of 22 non-isolated paediatric cases

CHAPTER 6.

Feeding and swallowing outcomes following mandibular distraction osteogenesis: an analysis of 22 non-isolated pediatric cases

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ABSTRACT

Patients with mandibular hypoplasia and upper airway obstruction are at an increased risk of feeding and swallowing difficulties. Little has been described regarding these outcomes following mandibular distraction. This study aimed to evaluate the effect of mandibular distraction on feeding and swallowing function. A retrospective study was performed on 22 non-isolated patients with severe upper airway obstruction treated with mandibular distraction. Median age at first mandibular distraction was 3.1 (interquartile range 2.3-6.0) years and median follow-up time was 3.5 (interquartile range 2.0-9.4) years. Prior to mandibular distraction, feeding difficulties were present in 18 patients. Swallowing difficulties were present in 20 patients, all of whom had problems in the oral phase of swallowing, whereas 11 patients had additional problems in the pharyngeal phase. Following mandibular distraction, at time of follow-up, feeding difficulties persisted in 13 patients. Swallowing difficulties in the oral phase remained present in all 20 patients, whereas pharyngeal phase problems persisted in seven patients. In conclusion, feeding and swallowing difficulties are highly prevalent in non-isolated patients and often persist following mandibular distraction. Moreover, it can be the reason that decannulation cannot be accomplished. Hence, awareness and close follow-up by a specialized speech therapist is of paramount importance.

INTRODUCTION

Mandibular hypoplasia (MH) is a common craniofacial abnormality that can occur in isolation (isolated MH). In non-isolated MH, comorbidities are present without a known syndrome (associated MH) or as part of a syndrome (syndromic MH). As MH includes a phenotypically heterogeneous cohort with a wide range in clinical expression, severity of MH varies considerably. Depending on severity, MH can cause subsequent posterior placement of the tongue base that results in upper airway obstruction (UAO) (1). Next to the respiratory difficulties are feeding difficulties (FD), which are present in up to 80% of the patients with MH and UAO (2-5). Patients with FD are unable to acquire sufficient oral intake, requiring additional tube feeding. One of the crucial components for oral intake is an adequate swallow function.

Swallowing is a complex neuromuscular mechanism of autonomic reflexes and active movements of several oropharyngeal structures by which food is transported from the mouth to the stomach. Normal swallowing consists of four phases, including: oral preparatory, oral, pharyngeal, and esophageal (6). In patients with MH, however, these phases can be affected due to several anatomical and functional deficits. Therefore, swallowing difficulties (SD) may contribute to inadequate oral intake. Mandibular distraction osteogenesis (MDO) can be effective in the treatment of severe tongue-based UAO (7, 8). By performing MDO, the mandible is gradually lengthened and, thereby, the tongue and suprahyoid muscles are displaced anteriorly increasing the pharyngeal airway volume (9, 10). A previous study performed in our center already reported a high prevalence of FD an SD in patients with facial dysostosis and severe UAO (5). Nonetheless, although the effect on anatomic structures is substantial by lengthening the mandible, objective outcomes on feeding and especially swallow function following MDO remain limited. Hence, we aimed to evaluate the effect of MDO on feeding abilities and swallowing function in complex, non-isolated children with MH.

METHODS

A retrospective study was conducted on children with severe UAO related to MH who underwent MDO in the Sophia Children's Hospital, the Netherlands between 2005 and 2020. This study was exempted from review by the local institutional Medical Ethical Review Board (MEC-2019-0396). Patients were included if they met all the following inclusion criteria: 1) severe UAO related to non- isolated MH. Severe UAO was defined as the presence of a tracheostomy tube or by the existence of severe Obstructive Sleep Apnea (OSA), defined as an obstructive-Apnea Hypopnea Index (oAHI) ≥10 objectified by a polysomnography (PSG) according to the American Academy of Sleep Medicine (AASM) and International Pediatric Otolaryngology Group (IPOG) consensus (11, 12); 2) MDO performed in the Sophia Children's Hospital; 3) age < 18 years at time of surgery. End of follow-up was defined as last outpatient visit, death or end of study.

Variables and outcome measurements

The following patient variables were extracted from electronic patient files: sex, date of birth, presence of a cleft palate, genetic diagnosis, concomitant craniofacial abnormalities, and relevant medical history.

Feeding outcomes

Feeding abilities were evaluated at the following time points: 1) prior to MDO, based on the latest information available prior to MDO; 2) during MDO, based on the information reported with the distraction device in situ; 3) after MDO, based on the information reported most proximate after removal of the distraction device; 4) at latest follow-up, based on the latest available information. Presence and severity of FD were stratified into three groups, according to the classification system of Caron et al. (2), as presented in **Table 1**.

Table 1. Classification of feeding difficulties

Classification	Type of FD	Criteria
1	No - Mild	Patient was able to be fully orally fed, irrespective of the consistency (i.e. pureed or solid foods) or feeding mechanism (i.e. Habermann bottle)
2	Moderate	Patient required additional tube-feeding next to oral feeding to acquire adequate intake*
3	Severe	Patient was fully dependent on tube feeding*

Classification of feeding difficulties according to Caron et al. (2). ***FD*** *= Feeding difficulties.*
** Percutaneous gastrostomy tube or nasogastric tube*

Swallowing outcomes

Reports on all swallowing evaluations by a specialized speech and language therapist (SLT) were collected and reviewed. In this study, we focused on the oral (including both the oral preparatory and oral phase) and pharyngeal phase of swallowing. Swallowing function was examined by an SLT during intake of different consistencies according to the International Dysphagia Diet Standardization Initiative (IDDSI) as presented in **Table 2** (13). Presence of SD was scored on the aforementioned time points according to the classification system as presented in **Table 3**.

Table 2. – International Dysphagia Diet Standardization Initiative (IDDSI)

IDDSI level	Consistency	Definition
0	**Thin** fluid	Flows like water
1	**Slightly thick** fluid	Thicker than water
2	**Mildly thick** fluid	Flows off a spoon
3	**Moderately thick** fluid/ **liquidized** food	Smooth/soft texture, can be eaten with spoon, cannot be eaten with fork
4	**Extremely thick** fluid/ **pureed** food	Commonly consumed with spoon, fork is possible. No chewing required
5	**Minced and Moist** food	Minimal chewing required, biting is not required. Can be shaped
6	**Soft and Bite-sized** food	Chewing is required before swallowing. Can be eaten with fork or spoon, knife not required to cut, but might be helpful
7	**Easy to chew and regular** food	Requires the ability to chew and bite, but does not necessarily require teeth

IDDSI framework - Overview of international terminology and definitions of dysphagia diets, according to Cichero et al. (13).

Table 3. Classification of swallowing difficulties

Classification	Type of SD	Criteria
1	**Oral phase***	Patient presented with one of the following: problems with sucking or lip closure, drooling/loss of liquid and/or food, problems with chewing, restricted or insufficient tongue movements, and/or excessive choking (gagging)
2	**Pharyngeal phase**	Patient presented with one of the following: problems with initiating swallow, delayed or absent swallow trigger, signs of laryngeal penetration or aspiration (change of voice, change of breathing sounds during cervical auscultation), frequent coughing, repeated airway infections, and/or difficulties in the coordination of sucking, swallowing, and breathing
3	**Both phases**	Patient endured problems in both the oral and pharyngeal phase of swallowing

Classification of swallowing difficulties, obtained during anamnesis or observed during examination by the SLT.
***SD** = Swallowing difficulties.*
**Oral phase includes oral preparatory phase and oral phase of swallowing.*

Respiratory outcomes:

Indication, date, and duration of respiratory support and subsequent airway interventions to treat other possible factors that could hinder decannulation were reported. When available, reasons for failed decannulation were noted.

Statistical Analysis

All analyses were performed using SPSS statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA, 2017). Descriptive statistics were reported as means (±SD) for normally distributed data or medians (interquartile range (IQR)) for non-normally distributed data.

RESULTS

Twenty-two patients were included in this study. All patients underwent bilateral MDO, except for one patient with unilateral craniofacial macrosomia (CFM). Eleven patients were diagnosed, clinically or genetically, with a syndrome (Treacher Collins syndrome (n=6), Nager syndrome (n=3), 22q11 deletion syndrome (n=1), and Trisomy 9 (n=1)). The remaining 11 patients presented with bilateral CFM (n=4), unilateral CFM (n=4), syngnathia (n=2), and bilateral cleft lip and palate (n=1). Nine (41%) patients had a cleft palate. Two patients previously underwent an MDO in another center, whereas two patients were referred to our center because of persistent UAO after decannulation and these patients were subsequently indicated for MDO in our center.

Table 4. Demographic data

	Total, n=22
Cleft palate present, n (%)	9 (40.9)
Airway support pre-MDO, n (%)	22 (100.0)
CPAP	3
O2	1
CPAP + O2	1
NPA + O2	1
Tracheostomy tube*	16
PEG tube, n(%)	16 (72.7)
Age at 1st MDO, median (IQR)	3.1 (2.3 - 6.0)
Age at time of follow-up, median (IQR)	8.9 (4.6 - 13.8)
Duration of follow-up after MDO, median (IQR)	3.5 (2.0 - 9.4)
2nd MDO, n (%)	6 (27.3)
Age (y) at 2nd MDO, median (IQR)	7.8 (7.0 - 11.1)
Decannulated**, n (%)	5 (31.3)
Age (y) at decannulation, median (IQR)	3.6 (2.6 - 4.5)
Time (y) to decannulation**, median (IQR)	0.8 (0.4-1.8)

Age and duration of follow-up are presented in years. ***IQR*** *= interquartile range.* ***MH*** *= Mandibular hypoplasia.* ***Pre-MDO*** *=Prior to MDO.* ***PEG tube*** *= Percutaneous gastrostomy tube.*
** Tracheostomy tube-dependent, including TCS (n=5), Nager Syndrome (n=3), 22q11 deletion syndrome (n=1), Trisomy 9 (n=1), syngnathia (n=2), bilateral cleft lip and palate (n=1). Bilateral CFM (n=3).*
***5/16 (31%) patients were decannulated, including TCS (n=3), 22q11 deletion syndrome (n=1), Trisomy 9 (n=1).*

Feeding outcomes

An overview of feeding status per patient is presented in **Figure 1**. Prior to MDO, four (18%) patients were classified with no-mild FD, five (23%) patients presented with moderate FD whilst 13 (59%) patients had severe FD, of whom all but one had a tracheostomy tube. Fourteen patients were fed by a percutaneous gastrostomy (PEG) tube, whereas the other four patients had a nasogastric tube. Feeding abilities shortly worsened during activating the distraction device in three patients due to an insufficient nutritional intake secondary to pain (n=2) or unsafe oral feeding due to worsening of swallow function with signs of aspiration (n=1). Feeding abilities recovered to pre-MDO status in all three patients (before device removal (n=2), during follow-up (n=1)). Directly after MDO, two patients showed an improved feeding ability. During follow-up, feeding abilities improved in another six patients due to improvement of swallowing function as these patients were guided by the SLT. At end of follow-up, nine (41%) out of 22 patients had no or mild FD, five (23%) patients had moderate FD, and eight (36%) patients, of whom seven patients had a tracheostomy tube, still had severe FD. All thirteen patients with remaining moderate or severe FD had a PEG-tube in situ.

Swallowing outcomes

An overview of swallow function per patient is presented in **Table 5** and **Figure 1**.

Prior to MDO, an affected swallow mechanism was present in 20 (91%) patients, in whom nine problems were limited to the oral phase of swallowing, whilst the other 11 patients had additional problems in the pharyngeal phase of swallowing. Ten out of these latter 11 patients had a tracheostomy tube prior to MDO. All nine patients with a disturbed oral phase of swallowing had problems with chewing and were unable to adequately form a bolus, secondary to malocclusion. These problems with chewing were seen while eating (hard) solid foods (IDDSI 7). Consequently, these patients were limited to the intake of pureed or soft solid food (IDDSI 4/5 n=7; IDDSI 6 n=2). The remaining 11 patients with problems in the pharyngeal phase of swallowing were therefore limited by practicing with intake of liquid foods only (IDDSI 0-3). Therefore, no conclusion on the ability to chew could be drawn. Five patients presented with transport problems subsequently leading to problems in the pharyngeal phase. Three of the latter five patients presented with premature spill into the pharynx (pre-spillage), whereas delayed swallow trigger was found in all five patients. Laryngeal penetration and/or aspiration was found in four of these five patients. The remaining six patients did not accept oral intake or swallowed too less, due to oral hypersensitivity and delayed (n=2) or absent swallow trigger (n=4). However, all six patients were suspected of having additional problems in the pharyngeal phase due to their medical history (e.g. absent swallow trigger, frequent coughing, repeated airway infections).

During MDO, drooling shortly increased in six patients (solely oral phase n=2; both phases n=4), but recovered to pre-distraction status at time of device removal in all procedures. Pharyngeal phase of swallowing deteriorated in four patients (laryngeal penetration and aspiration occurred (n=1) or aggravated (n=3)).

After MDO, SD were still present in 20 patients. In eight patients, problems were limited to problems with chewing. In the other 12 patients, problems in both phases of swallowing remained present.

During follow-up, problems with chewing remained present in all eight patients (IDDSI 4-5 n=5; IDDSI 6 n=3). In five patients, including the one with temporary deterioration of the pharyngeal phase, problems in the pharyngeal phase disappeared and these patients were able to eat food of soft solid consistencies (IDDSI 4-5 n=1; IDDSI 6 n=4). Since patients were able to eat solid foods, problems with chewing came forward. In two of the seven patients with remaining problems in the pharyngeal phase, laryngeal penetration and aspiration due to disturbed transport were still found when eating food of thin fluid consistencies (IDDSI 0,1). Five out of seven patients still did not accept oral intake or swallowed too less. Consequently, all 20 patients still had an affected swallow function at time of latest follow-up. Thirteen patients had problems with chewing secondary to malocclusion. The remaining seven patients, all with tracheostomy tube in situ except for one decannulated patient, still had problems in both phases of swallowing.

Table 5. Swallowing difficulties per phase during the intake of fluid foods

Presence of SD	Prior to MDO n=20	During MDO n=20	Post MDO n=20	End of follow-up n=20
THIN/THICK FLUID*				
Oral phase				
Oral motor difficulties	14	14	14	15
Problems with chewing**	9	8	8	13
Transport	5	6	6	2
Pre-spillage***	3	3	3	1
Oral hypersensitivity	6	6	6	5
Not possible to test*	0	0	0	0
Pharyngeal phase				
No problems	9	8	8	13
Pharyngeal phase problems	11	12	12	7
Swallow trigger				
Delayed	7	7	7	3
Absent	4	5	5	4
Penetration/Aspiration****	4	5	5	2
SOLID FOOD*				
Tested*	**n=9**	**n=8**	**n=8**	**n=13**
Oral phase				
Oral motor difficulties				
Problems with chewing**	9	8	8	13
Transport	0	0	0	0
Pre-spillage***	0	0	0	0
Oral hypersensitivity	0	0	0	0
Not possible to test*	11	12	12	7
Pharyngeal phase				
No problems	9	8	8	13
Not possible to test*	11	12	12	7

** If patients presented with problems in the pharyngeal phase of swallowing during the intake of fluid foods, they were not exposed to solid foods and were limited to practicing with solely foods of fluid consistency.*
***Problems with chewing could only be reported if patients were exposed to solid foods.*
****Patients with oral motor difficulties that also presented with pre-spillage.*
****** Patients with disturbed pharyngeal phase of swallowing that also presented with laryngeal penetration and/or aspiration*

Respiratory outcomes

Respiratory management and outcomes are presented in **Table 6** and **Figure 1**. At time of presentation, 16 out of 22 patients presented with a tracheostomy in situ, whilst the other six patients were treated with non- invasive respiratory support for their severe UAO. In ten patients, it was necessary to perform additional airway interventions that could possibly hinder decannulation: adenotonsillectomy (n=3), tonsillectomy (n=5), lingual tonsillectomy (n=1), and adenoidectomy (n=1). In nine patients, MDO was successful in terms of decannulation (n=5) or elimination of OSA (n=4). One patient, who was free of OSA after decannulation, deceased due to suffocation in a candy. The other four decannulated patients were free of OSA at time of follow-up. Eleven patients remained tracheostomy tube-dependent. One patient was decannulated in another center, but severe UAO reoccurred and this patient required replacement of a tracheostomy tube in combination with an MDO. Reasons for failed decannulation included unsafe intubation conditions (n=4), severe aspiration post distraction (n=3), inability to open their mouth due to syngnathia (n=2) or temporomandibular joint ankylosis (n=1), or practicing with capping the cannula at home (n=1).

Table 6. Respiratory management

	Prior to MDO		**End of follow-up**	
	No UAO	**UAO**	**No UAO**	**UAO**
No-trach n=6	0	6 CPAP (n=3) O2 (n=1) CPAP + O2 (n=1) NPA + O2 (n=1)	4*	2 CPAP (n=2)
Trach n=16	0	16 Trach (n=16)	5†	11 Trach (n=12)

No-trach *= group of patients with severe upper airway obstruction (UAO), but no tracheostomy tube in situ prior to MDO.* ***Trach*** *= group of patients with a tracheostomy tube in situ prior to MDO.* ***MDO*** *= Mandibular Distraction Osteogenesis.* ***CPAP****= Continuous Positive Airway Pressure.* ***NPA*** *= Nasopharyngeal Airway.* ***O2*** *= Oxygen supplementation.*

** One patient had a relapse of OSA and received CPAP for 1.48 years. One patient underwent BIMAX at the age of 21 to dissolve OSA. Both patient were free of respiratory symptoms at end of follow-up.*

† 1 patient died to suffocation in a sweet 1.7 years after decannulation.

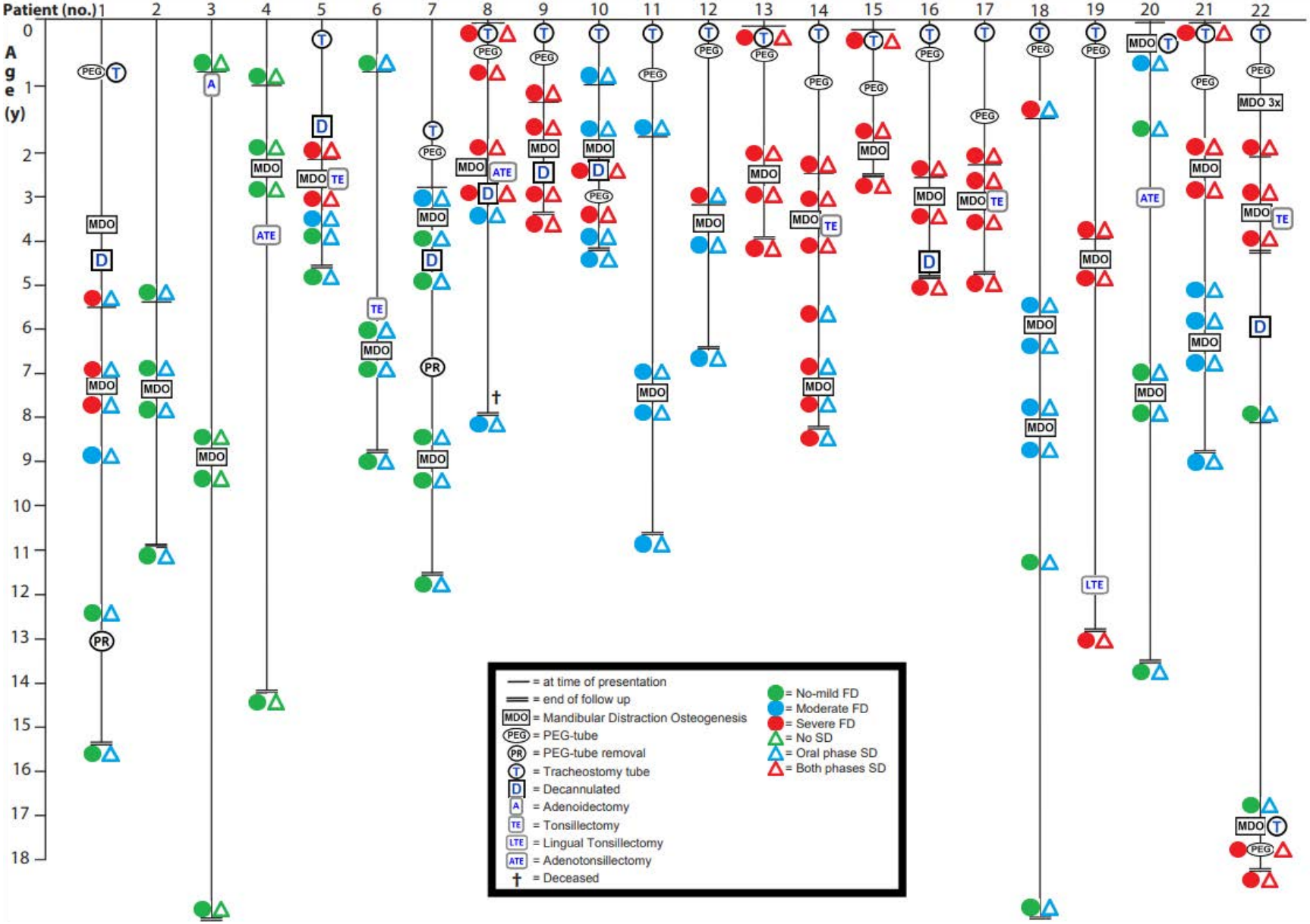

Figure 1. Feeding and swallowing difficulties in patients who underwent MDO

Overview of respiratory management, feeding abilities, and swallowing function in our patient population with mandibular hypoplasia and severe upper airway obstruction. ***FD*** *= Feeding difficulties.* ***SD*** *= Swallowing difficulties.* ***MDO*** *=Mandibular distraction osteogenesis.* ***PEG tube*** *= Percutaneous gastrostomy tube.* ***T*** *= Tracheostomy tube.* ***D*** *= Decannulation.* ***A*** *= Adenotomy.* ***TE*** *= Tonsillectomy.* ***ATE*** *= Adenotonsillectomy.*

DISCUSSION

In patients with MH, severity of feeding and swallowing difficulties is deemed to be associated with the severity of respiratory distress (2-4, 14, 15). Hence, patients with MH and severe UAO who are indicated for MDO are at an increased risk for FD and SD. As FD and SD are associated with severe or even life-threatening comorbidities, including malnutrition, failure to thrive, dehydration, aspiration, pneumonia, and chocking, awareness and early diagnosis are crucial for proper treatment and counselling. Furthermore, decannulation can only be provided if swallow function is sufficient. Therefore, the presence and severity of FD and SD should also be taken into account when describing outcomes of MDO. Nonetheless, this is one of the first studies that described both FD and SD as primary outcomes in patients with non-isolated MH following MDO.

Syndromic patients with MH are found to be 5 times more likely to endure FD (13). Since syndromic status is associated with neurological dysregulation, it might not only influence respiratory, but also feeding and swallowing mechanisms (16, 17). Accordingly, in this study of 22 children suffering from non-isolated MH, we found a high prevalence of FD (82%) and SD (91%) prior to MDO.

Following MDO, FD dissolved in five of the 18 patients with pre-existing FD, whereas FD remained present in 13 patients. Noteworthy, all four patients with no-mild FD prior to MDO remained able to be fully orally fed after MDO. As with FD, pre-existing SD seems to be a risk factor for the presence of SD following MDO. Problems in the oral phase persisted in all patients. However, these outcomes should be interpreted with caution as malocclusion (class 2 occlusion) is not corrected by MDO. Hence, problems with chewing do not resolve and may even aggravate after MDO due to overcorrection to a class 3 occlusion. Although problems in the pharyngeal phase of swallowing improved in four patients, they persisted in the majority of patients with pre-existing pharyngeal phase problems. Noteworthy, the pharyngeal phase worsened (temporarily) during MDO in 10 patients.

To the best of our knowledge, only two studies have focused on swallowing function following MDO so far. Both studies reported that all SD dissolved after MDO (18, 19). Normally, feeding and swallowing skills develop from the age of six months onwards as maturation of cortical afferent fibers starts (20). Nonetheless, both studies predominantly included isolated neonates with MH, all without neurological dysregulation. In this study of non-isolated patients in whom MDO was performed from 2 years of age onwards, we have found that pharyngeal phase problems often persisted. Moreover, we found temporary aggravation of feeding and swallowing function, which could be explained by the substantial effect on anatomic structures by lengthening the mandible.

Since feeding and swallowing skills strongly develop during the first year of life, intensive swallow therapy by an SLT during this first year of life can be of paramount importance and is therefore highly recommended in these non- isolated patients. Furthermore, although improvement of FD and SD is not always directly visible, we feel that all patients, whether (pre- existing) FD and SD are present or aggravated following MDO, should be continuously exposed to oral feeding, guided by an SLT, as this may improve long-term outcomes.

In patients with MH, difficulties in the oral and pharyngeal phase of swallowing can be caused by numerous anatomical and neurological factors, including presence of a cleft palate, adenoid/tonsil hypertrophy, problems with chewing due to malocclusion and limited tongue movements due to a reduced anatomical oropharyngeal airway space (6, 21, 22). Nonetheless, the exact pathogenesis of (temporary) pharyngeal problems remain undetermined and whether or not complete elimination of SD can be achieved, especially in those in whom problems are pre-existing. One can hypothesize that, as the mandibular and craniofacial bones are hypoplastic, the oropharyngeal muscles involved in swallowing are hypoplastic as well and cause a less powerful and less sufficient swallow function. Another possible explanation for SD in these patients is neurological dysregulation causing impaired motor function of the oropharyngeal muscles (23). Furthermore it is suggested that coordination between the oral and pharyngeal phase of swallowing might be disturbed which subsequently can cause, accompanied by suboptimal motor function of the esophagus and pharynx, problems in the pharyngeal phase of swallowing (23, 24). Although our numbers were too low and the studied group was too heterogeneous to differentiate between various conditions, we hypothesize that underlying pathway may also vary per syndrome. Investigating and understanding the exact pathophysiology of the different phases of swallowing in relation with feeding problems may aid in a more personalized and targeted treatment in these non-isolated patients.

Besides pre-existing SD and MDO itself, the presence of a tracheostomy tube can affect the swallowing mechanism as well. A study by Streppel et all. reported that 70% of the tracheostomized children have problems in at least one of the four stages of swallowing (25). It is believed that the tube tethers and desensitizes the larynx resulting in a decreased subglottic airway pressure. This decline in pressure subsequently causes an inefficient cough, which normally is used to prevent laryngeal penetration and aspiration (26). Ten of our 16 patients with a tracheostomy presented with problems in the pharyngeal phase of swallowing prior to MDO, whereas only one patient without tracheostomy tube had problems in the pharyngeal phase. Notwithstanding, the remaining six patients with a tracheostomy tube did not experience any problems in the pharyngeal phase. Moreover, in two decannulated patients

SD persisted. Consequently, it should be questioned whether these differences are caused by the presence of a tracheostomy tube alone or that patients with a tracheostomy tube are more severely affected compared to those without a tracheostomy tube. Whereas the policy in our center is to schedule MDO from the age of 2 years onwards to rely on adequate bone quality, in other centers MDO is performed during infancy (age < 1 year). It would be interesting to monitor FD and SD in a cohort of infants with similar diagnoses (non-isolated MH) in whom MDO has been performed to prevent a tracheostomy tube shortly after birth. Accordingly, the impact of an early tracheostomy tube on FD and SD could be further analyzed.

Since FD are closely related to respiratory outcomes, it is believed that elimination of UAO will reduce the presence and severity of FD (24). Nonetheless, this study demonstrated that no evident improvement of FD was seen after MDO, even if decannulation was achieved. Therefore, the direct association between breathing and feeding that was assumed previously, could not be confirmed by our study. This suggests that other factors interfere in this matter. We feel that as long as neurological dysregulation or anatomical deficits are present, elimination of the UAO alone by MDO will not eliminate the FD and SD in these patients (8).

Our study contains several limitations. Firstly, the retrospective design of our study results in missing data and lack of standardized reporting. Furthermore, the number of patients in whom an objective evaluation by a video fluoroscopic swallow study was performed was limited. From this point forward, we should be aware that airway, feeding, and swallowing evaluation should take place at more standardized time points in a more standardized way. Secondly, this study included a small and heterogeneous cohort. Although we hypothesize that some syndromes seem to do worse than others, our numbers were too low to draw conclusions regarding the different types of MH. Lastly, presence and severity of FD and SD varied considerably over time and in some patients improvement of FD and SD was seen only after a couple of years. Since the follow-up length was shorter in some patients, this could have given a biased estimate.

CONCLUSIONS

In conclusion, this study reported a high prevalence of FD and SD in patients with non-isolated MH with severe UAO, which often persists following MDO. The most important risk factors for poor feeding and swallowing outcomes after MDO were pre-existing FD and SD and patients who were tracheostomy tube- dependent. Although FD and SD may improve over time, temporary deterioration of feeding and swallow function can be found following MDO. Therefore, awareness, strict guidance, and swallow therapy by a specialized speech and language therapist prior to, during, and after MDO management are of paramount importance in these children. Nonetheless, the exact pathophysiology of feeding and swallowing (dys)function in these patients remains unknown. Future studies on long-term feeding and swallowing outcomes following MDO are required to expand knowledge and delineate underlying pathophysiology.

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General discussion

CHAPTER 7.

The aim of this thesis was to gain one step towards a better understanding of Robin sequence (RS) by focusing on the clinical characteristics and functional outcomes following management with special emphasis on mandibular distraction osteogenesis (MDO). Within this general discussion, the main study results will be discussed in the context of the recent literature, clinical recommendations will be presented, and future perspectives will be proposed.

MANDIBULAR HYPOPLASIA

DEFINING AND DIAGNOSING MANDIBULAR HYPOPLASIA

Forasmuch as mandibular hypoplasia (MH) is the defining and primary characteristic of RS, it has already been studied extensively (1). Nevertheless, defining and diagnosing MH remains challenging since there is currently no method generally accepted as the golden standard (2, 3). Furthermore, normal values in the pediatric population are lacking. Especially, data on mandibular development in both the normal population and the RS cohort during the first 4 years of life are missing. Consequently, diagnosis of MH is nowadays mostly based on clinical evaluation at first sight and therefore largely subjective (3, 4). By developing a new method, the Nasion- Mandibula ratio (NMRatio), using straightforward digital photography in **Chapter 2**, mandibular length and growth of RS patients was assessed in a simple, safe, and non-invasive way. Previous studies already demonstrated that linear and angular measurements on lateral photographs can be a reliable alternative in the characterization of facial morphology in adults and young adolescents (5-8). Considering that the NMRatio was found to be reliable and reproducible, according to the intra class correlation coefficient (ICC) for both interobserver (ICC=0.987) and intraobserver variability (ICC =0.808), the results of this study demonstrated that the NMRatio can be a practical alternative in clinical settings with limited resources, in patients in whom radiation is contraindicated or when anesthesia needs to be avoided, or in the event of large (longitudinal) research purposes. Nonetheless, as our measures were performed on lateral photographs, soft tissues were taken into account. Since we did not correct for potential confounders such as ethnicity and body mass index, this may have led to bias of our results (9).

Future studies should aim to develop or improve other non-invasive methods that depict mandibular position. Recent efforts have been made in 3D imaging by 3D facial photogrammetry, which is a fast, noninvasive and accurate way of imaging the complete face (10-12). By using predefined anatomical

landmarks, it enables detailed and precise analysis of facial morphologic characteristics, including the mandible. By comparing mandibular shape and volume of RS patients to healthy peers, it could conceivably differentiate individuals and may therefore be a valuable technique in the screening and diagnosis of the entities that involve RS (10, 13). This relatively new method is still under development. The first challenge is that young patients need to sit still and cooperate for at least several minutes to provide a proper and usable image. In addition, validation in large populations is required (13).

DELINEATING THE ROLE OF MANDIBULAR HYPOPLASIA IN RS

Although defining and diagnosing MH remains challenging, delineating the role of MH in relation to the functional outcome(s) can be a good step towards a better understanding of this clinical picture. By differentiating mandibular length, as expressed in the NMRatio, between non-severely affected RS patients and controls in **Chapter 2**, we examined if measuring MH could be of use next to the PSG in the diagnosis of RS. Previous studies on lateral cephalograms, CT, and MRI found remarkable differences in mandibular size and morphology between RS patients and controls (4, 14-18). Although our study on lateral photographs in 107 patients in **Chapter 2** also found significant differences between these non- severely affected RS patients and controls (isolated CP), no significant differences were found between RS patients and patients who were "diagnosed" with MH but who did not present with upper airway obstruction (UAO). Moreover, significant differences were found between "MH-only" patients and controls. In addition, no significant association is found between the severity of 'retrognathia', assessed from lateral view by clinical examination, and the severity of airway obstruction in non-surgically treated patients (14). Hence, mandibular length and/ or position are not one-on-one correlated with presence and severity of UAO: some patients can have a seemingly small mandible without UAO and vice versa. This underlines the importance of objectively assessing presence (and severity) of UAO by a polysomnography (PSG), avoiding an inaccurate (mis)diagnosis of RS. Nonetheless, as we did found differences between controls and RS patients, a seemingly small mandible should alert the clinician for the possibility of functional (e.g. respiratory and feeding) deficits.

Our results imply that, besides MH, other factors play a role in the respiratory status of (non-severely affected) RS patients. Muscular dysfunction, caused by neurological dysregulation (congenital/ permanent disturbed establishment of the neuromuscular organization), an immature breathing pattern, and/or hypotonia or hypoplasia of the oropharyngeal muscles, may lead to upper airway collapse due to the insufficiency to counteract against the gravity in supine position or the abrupt

intrathoracic pressure changes (19-24). Secondary airway abnormalities may further contribute to the complex, multifactorial obstruction in these patients, which are present in around 30% of the RS population (25).

The debate on mandibular catch-up growth, which seems to be dependent on the underlying pathophysiology, remains controversial (26-29). In our study amongst non-severely affected patients in **Chapter 2**, mandibular catch-up growth, which is suggested to be typically present in RS patients, could not be confirmed. Despite that the NMRatio decreased over time in all patients, significant differences remained present between RS patients and controls. These findings indicate that, although mandibular growth occurs (partially), these mandibles do not seem to demonstrate a compensating and faster growth compared to controls. As a consequence, these patients often end up with a small mandible, which is secondary to phenotypical variability rather than it is a pathology. Still, one should bear in mind that differentiating patients with an intrinsic growth deficit (malformed mandible) from those with a "normal" mandibular growth potential (deformational mandible) may be important for clinical decision-making and directing (personalized) management strategies (26-28). Remarkably, all included patients were sufficiently treated for their UAO, without surgical intervention. This emphasizes that other factors may play an important role in the resolution of UAO in these non-severely affected RS patients. This will be further discussed in the next part of this chapter.

Previous studies described substantial differences in mandibular shape and position between isolated and non- isolated RS patients (30, 31). Besides underlying mandibular pathophysiology, it is suggested that hypoplasia of the masticatory muscles affects mandibular position, shape, and size (32-35). In contrast to what many would assume, we found no significant differences between isolated and non-isolated RS patients in the first 3 months of life. Moreover, many severely affected syndromic RS patients have (severely) affected growth potentials, as found by our MDO studies (**Chapter 5 & 6**) that demonstrated that multiple MDO interventions are often required. Remarkably, however, in non-severely affected individuals, we found no significant differences in mandibular growth between isolated and non-isolated RS up till 4 years of age. This further support the claim that there is a wide range in severity of mandibular deformity within (non-isolated) RS patients and that a seemingly small mandible can be a result of a phenotypical variation rather than it automatically leads to morbidity.

Following this discussion, the question arises what the clinical relevance is of finding an objective diagnosis of MH in these non-severely affected patients. Since the MH itself does not seem to be a sensitive and specific predictor for the presence of UAO and severity of MH does not seem to add information on clinical severity, should we still need to strive for an (objective) diagnosis of MH in these non-severely affected patients.

TREATMENT ALGORITHM

Although several management algorithms have been proposed, there is still a lack of a widely accepted treatment approach (1, 36). One of the main causes for the lack of consensus on management strategy is that evidence for the effectiveness of interventions in RS patients is limited. Study populations are often small due to the low incidence rate. The combination with the high heterogeneity of the patient population further limits the generalizability of results in several RS subgroups. Furthermore, long-term outcomes are lacking due to the scarcity of (prospective) follow-up studies. Another explanation for the lack of a widely accepted treatment protocol is that studies that directly compare different, especially non-surgical, treatment modalities are limited. One of the reasons why it is challenging to compare outcomes is the absence of a uniform definition for successful treatment. Moreover, publication bias challenges the comparability of outcomes since most studies particularly report on successful outcomes, whilst studies that report on the unsuccessfulness of interventions are limited. The variety in study designs and the heterogeneity in study populations (e.g. genetics, ethnicity, and age) further complicate the comparability of outcomes. Nonetheless, one should take into account that direct comparison of interventions is difficult since it is unethical to withhold (the most appropriate type(s) of) respiratory support and base clinical decision-making on the desire to create a (control) group for study purposes. Lastly, RS patients often receive multiple treatment modalities, as was found in **Chapter 3**, with variable degrees of duration, which confounds the outcomes of treatment efficacy of each modality separately. Consequently, no widely accepted clinical cut-off values or classification criteria exist that guide clinicians in their decision. Additionally, uncertainty remains among factors that are associated with unfavorable outcomes, which further challenges directing optimal, widely-accepted, management strategies.

CLINICAL OUTCOMES AFTER (NON-) SURGICAL TREATMENT

RESPIRATORY DIAGNOSTIC PROCEDURES

The primary goal in the management of RS patients is to create and maintain a permissible and viable airway. Therapeutic decisions are therefore predominantly based on severity of respiratory distress in each individual patient. Timely recognition and diagnosis can be of paramount importance as untreated UAO is associated with considerable comorbidities that affect growth and development (37-41). Polysomnography (PSG) is considered as the golden standard to diagnose the presence and severity of UAO (38, 42). Grading (exact) severity of UAO, however, remains challenging, especially in (young) children (43-49). The difficulties in interpreting PSG in young infants obviates the need to take other parameters into account to decide about treatment. In this thesis (**Chapter 3**), we have used a combination of PSG variables (including oximetry data), capillary blood gas values, and clinical symptoms to determine the severity of UAO in infants. Significant differences were found in oximetry data (mean oxygen levels and oxygen saturation nadir) between patients treated with positional therapy and more severely affected patients who required respiratory support. Nevertheless, as it does not distinguish central events from obstructive events, solely relying on oximetry data can give an inaccurate (high) representation of the severity of obstruction (36, 43). Besides the presence of central apneas (immature breathing pattern), oximetry data can also be affected by age and by (winter) season (50, 51). Hence, although oximetry data can be helpful in the diagnosis of UAO or may be utilized when a PSG is not feasible to perform, it should be used with caution as a screening tool on its own due to its low sensitivity.

Besides difficulties in assessing severity of UAO in young infants, another issue in the diagnostic work-up for UAO is the timing. Severity and clinical presentation seem to vary considerably between and within patients over time. Firstly, we sometimes experience what we call a “honeymoon”: during the first days to weeks of life, these RS patients seem to do quite well (**Chapter 3)**. Notwithstanding, clinical signs of respiratory distress exhibit later in life or manifest as failure to thrive (52). Secondly, airway dimensions and thereby its patency, may improve naturally over time (53, 54). These findings are in accordance with our results presented in **Chapter 2 & 3**. We found that all patients were sufficiently treated for their UAO and did not require any further (surgical) intervention during the first year of life. Other factors that result in an improvement of respiratory distress should be considered, including the absolute increase of the airway volume by absolute growth of the neonatal airway volume and/ or a faster mandibular growth relatively to the tongue, resulting in a more anterior tongue position (55, 56). In addition, maturation of the breathing pattern may improve or even resolve airway collapsibility (22, 57). Still, it remains unknown what the exact impact of these interfering factors is on

UAO and how they evolve over time. Furthermore, they may also vary considerably among each individual RS patient. Delineating the type, and thus cause, of obstruction in patients with RS might be challenging but can be of great importance as it may change management strategies (58). Forasmuch as severity of UAO may vary over time as the child grows and after it receives treatment, objective reevaluation of the obstruction prior to, during, and after treatment is strongly suggested (37, 38). Moreover, although absolute airway size increases in RS patients, they may not reach the airway size of healthy children (59). Consequently, these children are at an increased risk of (re)developing UAO during childhood (e.g. enlarged adenoid and/or tonsils).

RESPIRATORY MANAGEMENT

According to the ethical principle "*do no further harm*", there is a universally accepted consensus that treatment should start with the least invasive options. However, timing and choice of secondary (and tertiary) treatment options vary across centers, depending on institutions' preferences and experiences (1, 4). In our center, we follow a protocol with a preferably non-surgical approach, which is reflected in this thesis. In agreement with clinical consensus reports, our management of infants with RS starts with positional therapy (4, 60). In patients with mild-moderate UAO who do not respond to positional therapy, non-surgical treatment is indicated which includes: Nasopharyngeal Airway (NPA), oxygen, High Flow Nasal Cannula (HFNC), and/or Non-Invasive Ventilation (NIV). To minimize morbidity associated with any form of surgical intervention, only those patients with acute and severe UAO or those with persistent airway obstruction despite non-surgical treatment are indicated for surgical intervention.

Whilst our protocol is predominantly based on a non-surgical approach, other studies advocate early surgical intervention since postponed surgery is claimed to be less effective in patients that eventually require surgery. Furthermore, it can avoid (life-long) complications associated with inadequately treated UAO (61-65). The results in **Chapter 3** demonstrated that the majority of patients were treated non- surgically (36/41) in our center and that these non-surgical modalities sufficiently treated the UAO. This further supports the finding that most patients seem to outgrow their respiratory compromise over time, avoiding the need of a more invasive, surgical, intervention. When surgery is done on these patients, the successful outcome might be unjustly attributed to the surgical intervention.

Non-isolated RS is associated with an increased risk of surgical intervention (66, 67). Notwithstanding, syndromic status is not one-to-one correlated with severe UAO as not all syndromic patients required surgical treatment (**Chapter 3 & 4**). Even more, some of our syndromic patients did not develop UAO at all. This further emphasizes the wide variability in clinical presentation and severity of UAO within the complex population of RS patients and advocates the important role of other factors in the presence and severity of respiratory distress, such as neurological status.

MANAGEMENT OF FEEDING DIFFICULTIES

A high prevalence of feeding difficulties (FD) was found in all our patients studied in **Chapter 3 & 4 & 6**, both treated non-surgically and surgically. The difference between these patient populations, however, was that FD persisted in the majority of severely affected patients that required surgical intervention whilst FD persisted in only 25% of the patients with mild-moderate UAO who did not require surgical intervention. These findings are in agreement with previous studies showing that the presence of severe UAO is associated with an increased risk of (severe and chronic) FD (52, 68). As feeding and breathing seem to be closely correlated, one would expect that (early) treatment of the UAO can reduce the FD and therefore decrease the amount of feeding intervention. Nonetheless, severe respiratory distress is often associated with chronic FD that will persist, regardless of timing and successfulness of airway intervention (52, 58, 68). Correspondingly, our findings in **Chapter 4 & 6** demonstrated that FD often persisted in patients with severe UAO (both Facial Dysostosis (FaD) patients and patients treated with MDO). Notwithstanding, although FD and UAO are closely related and severe UAO is often associated with increased duration of additional tube feeding, the correlation of UAO and severity and duration of FD is not linear (69). This, again, underlines the challenging clinical diversity within RS individuals. Concurrent with other studies, our findings demonstrated that, besides severity of UAO, the presence of non-isolated RS is associated with an increased risk of (severe and) chronic FD (68, 70-72). More specifically, we found remarkable differences between our FaD patients and our non-isolated MH patients who were treated with MDO: 54% of the patients with FaD had persisting FD whilst in 72% of the non- isolated patients who were treated with MDO the FD persisted. This implies that, as with respiratory difficulties, the presence of underlying comorbidities (e.g. neurological dysregulation, anatomical abnormalities, swallowing difficulties) seems to play a more important role in the feeding status of MH patients rather than syndromic status only. Delineating the exact cause is therefore of paramount importance for targeted treatment in the child with feeding difficulties.

MANAGEMENT OF SWALLOWING DIFFICULTIES

In patients with MH, multiple anatomical factors can cause SD (e.g. cleft palate, adenoid/tonsil hypertrophy, malocclusion, reduced oropharyngeal space, and hypoplasia of the oro- and pharyngeal muscles) (20, 69, 73- 75). Even more challenging are the problems in the pharyngeal phase of swallowing as the exact pathogenesis of (temporary) pharyngeal problems remains undetermined. It is suggested that neurological dysregulation is a key factor which can either be caused by immature coordination or by permanent disturbance of the swallowing mechanism (22, 69, 76, 77). Neuromuscular dysregulation can be present at the level of the central nervous system, but it can also be caused by dysregulation at the peripheral (muscular) level. Although derived from different structures (muscles derive from endoderm, nerves derive from ectoderm + neurocrest cells), both structures might be affected as they develop from the same pharyngeal arch during development (78). Therefore, the combination of both hypoplastic musculature and the presence of neurological dysregulation can be present as well, leaving the management of SD extra challenging.

As with FD, non-isolated RS is associated with an increased risk of SD (75). Accordingly, this thesis found a high prevalence of SD in both FaD patients (n=15/18) and non-isolated MH patients treated with MDO (n=20/22) that persisted in almost all patients (FaD n=14/15; MDO n=20/20). Nonetheless, the exact pathologic mechanism of these oropharyngeal lesions remains unclear.

Since the greatest advancements in the development of feeding and swallowing skills take place during the first year of life, proper education and practice during this first year(s) of life are critical for the adequate development of feeding and swallowing skills. Inadequate development during this first year of life can result in long-term difficulties (75, 79-81). Forasmuch as the infant nervous system is prepared for the development of new motor skills at each stage separately, repetitive feeding exposure at every stage is essential to develop each stage independently. Infants who are not able to sufficiently suck and swallow during the first months of life will not necessarily have feeding problems during spoon feeding, as long as they get exposed to feeding during that specific stage. This was supported by our findings in **Chapter 4 & 6**, which demonstrated that SD may improve over time. Feeding and swallowing function in RS patients will be further discussed in the paragraph on **Mandibular Distraction Osteogenesis.**

MANAGEMENT OF GROWTH

Patients with RS are at an increased risk of impaired growth. Next to the limited intake secondary to the abovementioned affected oral feeding skills, the increased energy expenditure to work against an obstructive airway may result in elevated energy demands. Furthermore, limited sleep efficiency, inadequate sleep time, and chronic hypoxic exposure subsequently trigger cellular and metabolic mechanisms that extract energy away from growth pathways (82). Compared to isolated CP patients, RS patients have a significantly lower weight and length, and impaired growth rates during their first (2) year(s) of life (83, 84). Further evidence in this respect follows from the findings in **Chapter 3 & 4**, which demonstrated that most patients with MH remained at a lower standard deviation score (SDS) weight for age (WFA) during their first year of life compared to their healthy peers. Moreover, WFA of non-surgically treated RS patients remained declining during the first year of life (0.40 to -0.33 to -1.03, respectively). Besides delayed weight growth, SDS height for age (HFA) was also markedly lower in both RS patients and FaD patients (median SDS HFA: -0.714 and -1.15, respectively) during the first (2) year(s) of life compared to healthy children of the same age. Remarkably, weight in FaD patients improved to almost normal (SDS WFH -0.14) at the end of follow-up (up to 18 years of age), whilst the height of FaD patients remained considerably lower compared to healthy peers (SDS HFA −1.10). Nonetheless, one should consider that some specific syndromes are associated with an expected growth that lays below the normative height velocity. It remains unknown whether or not there is an inherited growth deficit associated with particular genetic exposure in RS patients or that other factors interfere with appropriate growth, such as insufficient intake secondary to the FD and SD or underlying (co)morbidities.

Besides, in **Chapter 3 & 4** we found that malnutrition during the first year(s) of life occurred more often in severely affected patients with FaD (44%) than in our non-surgically treated RS patients (20%). During further pediatric development, even up to 90% of the FaD patients endured at least one form of malnutrition (e.g. acute and/or chronic). These findings are alarming and warrant attention. Although it might not directly treat the cause of malnutrition, referral to a dietician is already strongly recommended to meet sufficient energy requirements in order to avoid malnutrition and subsequent failure to thrive (85). However, despite the growing attention to feeding and growth outcomes, implementation of a hypercaloric diet or referral to a dietician does not (yet) seem to be widely accepted in the management algorithm of RS (86, 87). Correspondingly, our findings in **Chapter 3** demonstrated that although a high prevalence of FD and impaired growth was found, less than half of our patients (44%) were consulted by a dietician and only 53% of our patients received feeding with extra calories and/or extra protein.

FACIAL DYSOSTOSIS

A very complex and challenging patient population within the spectrum of patients with MH studied in this thesis are patients that present with facial dysostosis (FaD) (**Chapter 4**). Besides that FaD patients are at an increased risk of having severe UAO, one of the most important findings of this chapter was that respiratory management was successful in treating the UAO in only 4/18 of our patients (22%). Recent studies reported similar success rates (39% and 21%) among FaD patients (35, 88). Another reason why treatment of these patients is challenging is that long-term outcomes are also a matter of concern. UAO reoccurred (n=3) and/or persisted (n=12) after initial treatment in 15 of our 18 included patients (83%), requiring a secondary airway intervention or resulting in persistent tracheostomy-dependency, which is assumed to be caused by the lack of mandibular growth potential (34, 88, 89). Along with respiratory outcomes, feeding and growth outcomes in these patients are also worrisome. In **Chapter 4**, we found a high prevalence of FD and SD that often persisted, despite guidance by a specialist (SSLT and/or dietician). Aside from the fact that these patients may suffer from several functional problems, there is also a very wide range in clinical severity among FaD patients. In our clinical experience, we simultaneously notice patients with FaD without functional impairments. Additionally, we have found some remarkable differences between FaD subgroups: patients with Nager syndrome seem to do worse compared to those with Treacher-Collins syndrome. Notwithstanding, although our outcomes on FaD patients were of clinical importance, our findings should be interpreted with caution due to the small study population.

MANDIBULAR DISTRACTION OSTEOGNESIS

ANATOMICAL AIRWAY OUTCOMES FOLLOWING MDO

In the last part of this thesis, we focused on the functional outcomes following mandibular distraction osteogenesis (MDO). Although many studies reported on the outcomes after MDO, there is still a lack of consensus on the indications for surgery, timing, and treatment protocol due to the variety of study populations and surgical techniques (90). Accordingly, MDO management currently varies across centers and countries and is predominantly based on a specific center's preference (60, 90). Previous studies have reported success rates up to 95% after MDO in isolated RS patients (67).

On the contrary, the results of our studies in **Chapters 4 & 5 & 6** demonstrated that MDO was successful in terms of resolution of UAO or decannulation in less than half (33-41%) of our patients. These low success rates are most likely explained by the fact that all our patients presented with non-isolated MH, which often occurs in combination with other morbidities, including neurological dysregulation, multilevel obstruction (e.g. choanal atresia, congenital tracheal anomalies), or acquired tube-related complications, that are not solved with mandibular lengthening alone (67, 91-94).

In **Chapter 5**, we have focused on the anatomical airway outcomes, as found by drug induced sleep endoscopy (DISE), following MDO. According to the findings of this study among 22 non-isolated MH patients, the question remains why sufficient elongation of the mandible does not always result in functional improvement of the UAO. One might distinguish two groups of patients: those with and those without improvement of the oropharyngeal airway space (OAS):

1. In those patients in whom the OAS improved, concomitant comorbidities hindered resolution of the airway problems such as multilevel obstruction, unsafe swallow function, resistance against capping the cannula, and unsafe intubation conditions.
2. In those patients without improvement of the OAS, MDO fails to (sufficiently) improve anatomical airway, despite mandibular lengthening. It conveys the impression that there is something fundamental in this population that we fail to address with MDO. Although our numbers were too low to draw definite conclusions, our findings imply that this might be inherent to some specific syndromes in which extreme mandibular hypoplasia is present (e.g. Nager syndrome).

Previous studies already remarked the importance of performing endoscopy and assessing laryngoscopy grades during MDO management (67, 95). In accordance, our results in **Chapter 5** demonstrated that distinguishing between the two types of patients can be of paramount importance in understanding the differences in functional airway outcomes after MDO and therefore directing appropriate management strategies. Noteworthy, two patients with promising PSG outcomes but unfavorable endoscopy outcomes following MDO demonstrated severe respiratory distress after decannulation and required immediate recannulation to provide a safe and accurate airway. These findings further underline the importance to assess anatomical airway outcomes during MDO management.

Notwithstanding, one should bear in mind that, although DISE allows visualization of the anatomical airway, assessing and grading the severity of obstruction is still subjected to inter-and intra-observer variability (96). Moreover, the method of anesthesia and depth of sedation during the investigation will also influence endoscopic findings (97, 98). As long as no method to measure exact volumetric airway is available, interpretation of endoscopy always carries a risk of bias. Therefore, outcome of endoscopy and DISE should be assessed with care and should be interpreted in combination with other factors (e.g. clinical symptoms, PSG characteristics).

FEEDING AND SWALLOWING IN MDO

An important factor in the low success rates for decannulation after MDO is the presence of an unsafe swallow mechanism. The results in **Chapters 4 & 6** demonstrated that if swallowing difficulties were present prior to MDO, they are very likely to persist on the long-term, especially in non-isolated, severely affected MH patients. Moreover, the presence of a tracheostomy tube was suggested to have a negative impact on (long-term) swallow function, which is in agreement with the studies of Streppel et al. (99, 100). In patients with MH, it is assumed that the posterior placement of the tongue (glossoptosis) is a crucial component in (persisting) swallowing difficulties (101). By lengthening the mandible, the oral(pharyngeal) space will increase which should allow expanded functional movements of the tongue, resulting in improvement of the (oral phase of the) swallowing mechanism. In contrast to what many would assume, problems in the oral phase of swallowing persisted in almost all patients (FaD n=14/15; MDO n=20/20), whilst problems in the pharyngeal phase of swallowing did improve in around half of the patients (FaD n=3/7; MDO n=7/11). Although several concomitant anatomical factors can cause or aggravate problems in the oral phase of swallowing (e.g. malocclusion, cleft palate, adenoid/tonsil hypertrophy), these are often (directly) treatable issues. For this reason, we feel that this was not the primary reason that SD persisted or hindered decannulation. Having looked at the findings above, other factors are probably interfering in the persisting SD in these patients. Airway obstruction is also presumed to play a key factor in causing swallowing disorders (101). Since FD and SD are closely related to respiratory outcomes, one would expect that MDO results in an increased upper airway tract and hereby improving or resolving the UAO (71). Surprisingly, however, the results of our studies in **Chapter 4 & 6** demonstrated the lack of improvement or even aggravation in feeding and swallowing function despite respiratory improvement after MDO. Since the direct association between lengthening of the mandible and breathing and feeding/ swallowing could not be confirmed by our study, this further supports the hypothesis that other factors (e.g. neurological dysregulation and/or hypoplasia of the oropharyngeal muscles) interfere in the swallowing status of patients with MH.

Moreover, temporary aggravation of feeding and/ or swallowing function was found in **Chapter 6**. Mandibular lengthening has a substantial effect on the anatomical structures involved in swallowing. One can hypothesize that, as changes occur in a relatively short period, children need time to adapt or even relearn swallowing after this significant change in anatomical position. Hence, although feeding and swallowing function may worsen following MDO, patients still need to be exposed to oral feeding, guided by an SSLT. Continuous stimulation swallowing after adaption to the new oral anatomy may improve long- term swallow outcomes (79-81). Just as with respiratory outcomes, it remains unknown why some patients have worse feeding and swallowing function.

MULTIDISCIPLINARY TEAM APPROACH

The multiple functional aspects (e.g. respiratory, feeding, swallowing, growth) in this complex patient population remain challenging and emphasize the requirement of a multidisciplinary approach, preferably in a specialized center. This team of specialists should include at least pediatricians, oral & maxillofacial surgeons, otolaryngologists, plastic surgeons, orthodontists, speech and language therapists, and psychologists (102). Furthermore, the clinical geneticist has to be consulted in an early stage to identify associated malformations or comorbidities that might influence diagnosis, clinical decision-making, and prognosis. Since genetic diagnostics continue to expand, clinical re-evaluation and genetic (up-to-date) testing can be of paramount importance in the diagnostic workup.

LIMITATIONS

Some limitations should be acknowledged when interpreting the results. First, the retrospective design of our studies may have resulted in incomplete or missing data. Second, our data solely reflects upon the outcomes of our own treatment protocol. Since management protocols vary within centers, this carries a risk of bias. Third, the relatively low incidence of RS in combination with the heterogeneity of the patient population resulted in small sample sizes. We therefore included the whole spectrum of patients with mandibular hypoplasia suffering from (severe) UAO. Although they have a common trait of MH, this is such a heterogenic cohort, comprising a wide spectrum of syndromes and comorbidities that affect numerous different physiological pathways, that it is very hard to draw definite conclusions.

CONCLUSIONS & CLINICAL RECOMMENDATIONS

By focusing on the functional outcomes following non-surgical and surgical treatment, this thesis aimed to improve knowledge on the clinical characteristics of RS patients. According to our findings, the following conclusions and clinical recommendations can be drawn:

1. As long as diagnosing MH is largely subjective and does not draw any conclusions regarding functional outcomes, the primary focus should lay on whether or not the MH causes (significant) functional problems (e.g. respiratory problems, restricted tongue movement for swallowing, malocclusion) rather than (an attempt to) make a diagnosis of MH in each individual patient (**Chapter 2**).
2. Due to the lack of a uniform definition and the fluctuation in severity of UAO over time in each individual patient, objectifying severity of UAO is challenging, especially in neonates. All PSG parameters, capillary blood gas values, and clinical symptoms should be taken into account when classifying severity of UAO in young infants (**Chapter 3**).
3. Given the relatively high prevalence of FD, SD, and malnutrition in RS patients (**Chapter 3 & 4 & 6**), routine weight and height evaluation on standardized time points is required and early assessment of feeding and swallowing function by an SSLT is of paramount importance in all RS patients. Furthermore, to facilitate sufficient nutritional requirements and promote adequate growth, a dietician should be involved in the treatment of RS patients (**Chapter 3**).
4. Clinicians should be alert on the presence and reoccurrence of (severe) breathing problems and concomitant feeding and swallowing problems in FaD patients and these disorders should be seen as a separate entity. Accordingly, close follow-up by a specialized craniofacial team is indispensable (**Chapter 4**).
5. Clinicians should be tentative in counseling parents and patients for MDO. Risk factors for poor outcomes after MDO include a non-isolated status, presence of a tracheostomy tube, and an insufficient swallow function that is pre-operatively existing (**Chapter 5 & 6**).
6. In some patients, MDO seems to be unable to improve the airway, despite sufficient lengthening of the mandible. Standardized DISE performance and assessment of the Cormack-Lehane score during MDO management should be implemented in the MDO-protocol, preferably with the presence of video footage (**Chapter 5**).
7. A high prevalence of FD and SD was found in non-isolated RS patients that undergo MDO and often persists or may even aggravate following MDO. Close follow-up by an SSLT during MDO management is mandatory (**Chapter 6**).
8. The multiple functional aspects (e.g. respiratory, feeding, swallowing, growth) emphasize the need for a multidisciplinary approach, preferably in a specialized center. Considering the variability in clinical presentation, management should be tailored to the specific needs of each individual RS patient.

FUTURE RESEARCH PERSPECTIVES

In the next couple of years, RS patients and their parents will be invited for participation in research trajectories and therefore the RS cohort will continue to expand. Recent efforts have been made to improve the consistency of data gathering and reporting by developing widely accepted outcome measures (e.g. ICHOM), that are consistently reported according to validated grading scales and stored in universally used data capture systems. Furthermore, collaborative efforts among craniofacial institutes should be initiated to generate larger study samples in order to enhance reliability and generalizability of results. Prospective follow- up studies are required to give better insights into the long-term outcomes. Both the amount and the quality of data will increase, which will offer compelling possibilities for further research.

Understanding the functional outcomes in RS is a priority. While writing this thesis, unravelling each functional characteristic was found to be challenging due to the heterogeneity in etiology, the wide range in clinical severity, the lack of a uniform definition, and the absence of homogeneously reported objective outcomes. Still, there are a lot of uncertainties among the clinical characteristics in RS patients. Elucidating each characteristic separately would improve overall management and will eventually optimize care. Based on the findings in literature and the results of our studies, several research questions can be proposed.

First, although defining and diagnosing of MH is (clinically) questioned, improving knowledge on the role of MH in relation to the functional outcome(s) may contribute to a better understanding of RS. In future, one should seek for the development and improvement of other diagnostic methods that accurately determine MH. These methods should aim to be easily accessible and non-invasive, from which the 3D- photogrammetry seems the most promising method.

Second, considering the high prevalence of FD and SD in RS patients, future studies should focus on identifying risk factors that are associated with the presence, but especially persistence of FD and SD. In order to do so, feeding and swallowing function should be analyzed in different (non-isolated) patient populations. Evaluation should be done following a standardized and evidence-based protocol, which preferably includes the performance of objective diagnostic measures including a VFSS and/or FEES that are scored according to validated and widely accepted scales.

Third, factors that are associated with impaired growth should be established. Although a few studies have described growth outcomes in patients with RS on the short term, evidence on long-term growth outcomes is currently lacking. On that account, longitudinal studies that focus on the FD and long-term growth trajectories of both isolated and non-isolated RS patients are required.

Fourth, prospective, longitudinal studies on different (non-surgical) treatment modalities should aid in optimizing management strategies. Whilst our protocol is predominantly based on a non-surgical approach that should outweigh the potential risks of a surgical procedure, other studies advocate early surgical intervention to avoid (life-long) complications associated with inadequately treated UAO. To optimize care, both the short (e.g. respiratory, feeding, and growth) and the long-term (neurocognitive development) outcomes of surgical and non-surgical management strategies should be addressed. In addition, quality of life of both the patient and the parents should be taken into account. Furthermore, consecutively investigating underlying (genetic) pathologies will contribute to a better understanding of the etiology of both isolated and non-isolated RS. By differentiating patients etiologically, treatment can be more targeted to the individual patient, outcomes might be better understood, and eventually better predicted. Moreover, elucidating underlying genetic pathophysiology will also contribute to a better organization of follow-up, tailored to the specific needs of the individual RS patients.

Fifth, throughout writing this thesis, we experienced that the group of patients with FaD is a very complex subpopulation that should be addressed with caution. Future studies in a large subset of FaD patients are highly recommended and should assess long-term functional outcomes in terms of respiratory, feeding, swallowing, and growth. Furthermore, as we found some remarkable differences within FaD subpopulations, comparing outcomes between various syndromes could be of great value in optimizing the care of these patients.

Last, one of the principal topics in this thesis was mandibular distraction osteogenesis (MDO). Although many studies already reported on the surgical procedure and the subsequent clinical outcomes, a lot of dissimilarities remain among this procedure throughout centers and specialists. To improve overall MDO management, studies should aim to identify what patient characteristics (e.g. syndromic subtypes, (pre-MDO) mandibular and upper airway volume, position of the hyoid bone) are associated with poor outcomes. Most strikingly, the underlying pathophysiology following MDO remains undetermined. Delineating upper airway morphology following MDO is highly recommended to

comprehend the change in airway shape and volume following MDO and to figure out whether anatomy (e.g. hyoid bone shape and position) is relevant for the (functional) outcome. The use of DISE, MRI, and CT-scans with 3D reconstructions have already been suggested and should be included in these assessments. In addition, future studies should aim to investigate underlying swallow pathophysiology following MDO. Possible helpful diagnostic techniques may include an electromyography (EMG), as this is a noninvasive and inexpensive technique to evaluate muscle activity during swallowing. Furthermore, cine MRI can be used to identify shape, volume (length, size, and thickness), and position of the involved anatomical structures. Currently we are implementing a prospective study on QOL outcomes around the MDO- procedure. Future studies should evaluate these QOL outcomes following MDO.

Although beyond the scope of this thesis, we found some gaps in literature that can be interesting for future research:

- Literature on quality of life (QOL) is currently limited. Understanding the QOL of both RS patients and their parents would aid in improving management strategies.
- Improving prenatal diagnostic modalities will contribute to a higher detection rate. Identifying RS patients, especially patients who are at risk for immediate and severe UAO after birth, offers the opportunity to provide well-anticipated delivery by an experienced multidisciplinary team which may avoid subsequent complications. Besides, prenatal counseling prepares parents and their families and may therefore avoid anxiety, stress, and disappointment.
- Evidence on long-term neurocognitive outcomes is lacking. Up till now, it remains unclear to what extent neurological impairment may be caused by (chronic) exposure to hypoxia, secondary to UAO, or that there is an inherent problem in these RS patients causing underlying developmental delays (of variable severity). Prospective longitudinal studies are required to address long-term neurocognitive outcomes.

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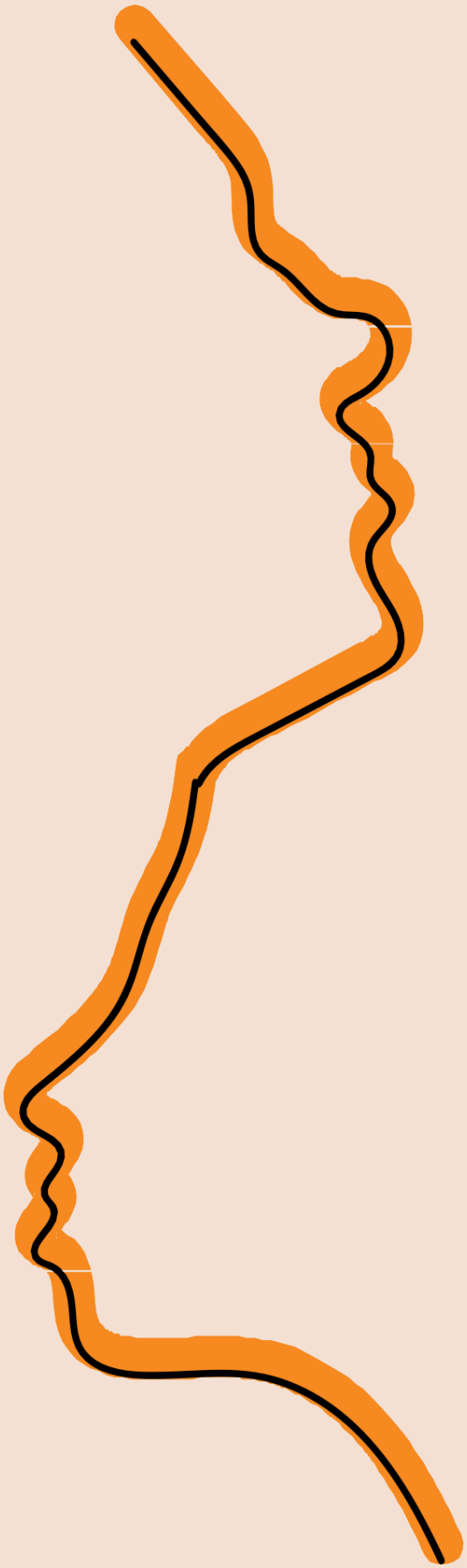


Summary

CHAPTER 8.

This thesis aimed to create a better understanding of Robin sequence (RS) by focusing on the clinical characteristics and functional outcomes following treatment in our center. In this way, we endeavor to add valuable information to the current knowledge of RS and therefore contribute to an improved quality of care for these patients.

In **Chapter 1,** a general introduction, including background information on the clinical implications of Robin Sequence, is provided. Furthermore, a short outline of the chapters and the subsequent aims are presented. Robin Sequence (RS) is a congenital craniofacial abnormality characterized by the typical triad of symptoms, including mandibular hypoplasia (MH), glossoptosis, and a varying degree of upper airway obstruction (UAO). A cleft palate occurs in around 90% of the patients, whilst feeding difficulties, with or without concomitant swallowing difficulties, are present in approximately 80% of the patients. RS may occur in isolation (isolated RS), but can also be present in combination with other abnormalities or syndromes (non-isolated RS). The wide range in clinical presentation in combination with etiologic heterogeneity continuously challenge clinicians, leaving the Robin sequence triad complex and still poorly understood.

Since mandibular hypoplasia (MH) is the defining characteristic of RS, delineating the role of MH can be the first step towards a better understanding of this challenging condition. Therefore, we wanted to examine if measuring MH is of added value, next to the polysomnography (PSG), in the diagnosis of RS. Currently, there is no golden standard to diagnose the presence and severity of MH. Hence, diagnosis is based on clinical evaluation on sight and therefore still largely subjective.

In **Chapter 2**, a new, non-invasive, simple, and safe method using straight forward digital photography to assess mandibular length is presented. By differentiating mandibular length of RS patients to that of controls, we endeavored to create more perspicuity on the role of MH in the diagnosis of RS. Mandibular length was assessed by determining the position of the mandible relatively to the nasion, which was scored as the Nasion Mandibula Ratio (**NMRatio**). The results among 107 infants demonstrated that, according to the intra class correlation coefficient for both interobserver and intraobserver variability (r=0.987 and r=0.808, respectively), the NMRatio is a reliable and reproducible method. Notwithstanding, no significant differences were found between RS patients and patients who were “diagnosed” with MH but who did not present with UAO. Hence, mandibular length, as expressed in the NMRatio, was found to be an inaccurate predictor for the presence of UAO in the first

3 months of life. Consequently, mandibular length can solely be used as a guide in the direction of the diagnosis of RS, but a PSG always needs to be performed to objectify and confirm the presence and severity of UAO.

In the majority of RS patients, airway obstruction seems to improve over time without respiratory intervention or mandibular correction, which is suggested to be caused by the presence of the so-called mandibular "catch- up growth". Still, a lot of controversy remains among this phenomenon in literature. Therefore, we aimed to evaluate mandibular growth in patients with RS. Our findings in **Chapter 2** demonstrated that mandibular size of RS patients did not seem to reach values of "normal" infants up till 4 years of age. Accordingly, mandibular catch-up growth, that is suggested to be typically present in RS patients, could not be confirmed by our study.

The following part of this thesis focuses on the functional outcomes following both non-surgical and surgical management in our center. Currently, management of patients with RS remains controversial and treatment protocols vary per center, depending on the institutions' preferences. According to the ethical principle *'do not further harm'*, we follow a protocol with a preferably non-surgical approach: most patients with moderate to severe UAO who are not directly in need of a tracheostomy are treated with non-surgical modalities (e.g. NPA, CPAP, oxygen). In this way, we aim to minimize the number of patients that will undergo a surgical intervention and its' associated comorbidities.

In **Chapter 3**, the functional outcomes following our non-surgical management are evaluated. This study among 36 infants who were prospectively followed during their first year of life, demonstrated a near normalization of respiratory parameters. From start treatment (PSG 1), to stop treatment (PSG 2), to the age of 1 year (PSG 3), the median obstructive apnea hypopnea index decreased from 7.0 to 1.1 to 0.5. Furthermore, during this first year of life, symptoms of respiratory distress dissolved, oxygen levels enhanced, and capillary blood gas values improved to approximately normal. These results imply that our non-surgical approach seems to be successful on the functional airway. Besides respiratory problems, feeding difficulties (FD) were found to be highly prevalent in this patient population (86%). Although treatment of the UAO seemed to be sufficient, FD persisted in 29% of the patients that presented with FD and 20% of the patients were still malnourished at the age of 1 year.

Growth was also a matter of concern. Both the weight for age (WFA) and height for age (HFA), expressed in a standard deviation score (SDS), were considerably lower compared to healthy peers at the age of 1 year (-1.03 and -0.71, respectively). Even more, SDS WFA remained declining during that first year of life: from -0.40 (PSG 1) to -0.33 (PSG 2) to -1.03 (PSG 3), respectively. These findings are alarming and demonstrate the urgency of close feeding and weight evaluation in RS patients.

In **Chapter 4**, functional outcomes regarding airway, feeding, and growth in 18 patients with Facial dysostosis (FaD) following management in our center are described. FaD is a rare congenital craniofacial abnormality of the skeletal and soft tissues caused by abnormal development of the pharyngeal arches during embryogenesis. Patients with FaD were found to have a high risk (50%) to develop severe UAO and these patients often demonstrate impaired functional outcomes in terms of respiration, feeding, swallowing, and growth. In our center, we preferably follow a conservative protocol and patients are treated non-surgically, if possible. However, the majority of our FaD patients with severe UAO (eventually) required surgical intervention (89%). Feeding difficulties were present in 72% and persisted in 54% of the patients with FD, whilst swallowing difficulties (SD) were present in 83% and persisted in 93% of the patients with SD. Twenty-five percent of the patients remained malnourished at end of follow-up, despite additional tube feeding. Moreover, we found that palatal closure gives a considerable risk of reoccurrence or worsening of UAO, despite good results of the PSG with an orthodontic plate to simulate closure. Noteworthy, two patients deceased during follow-up. Conclusively, FaD was found to be a very complex subgroup of patients with syndromic RS who do not have the tendency to naturally improve over time. Furthermore, long-term functional outcomes are often poor. Therefore, FaD should be considered as a unique entity. Close follow-up by a specialized multidisciplinary craniofacial team is highly recommended.

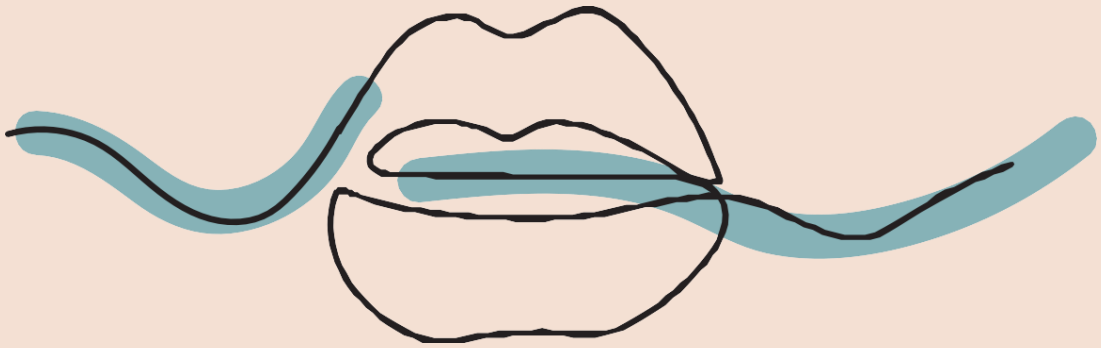
The last part of this thesis describes the functional outcomes following Mandibular Distraction Osteogenesis (MDO) in our center. Despite the numerous reports on MDO in literature, there is no consensus on the indications for surgery, timing and choice of surgical technique due to the differences in study methods and the heterogeneity of study populations. Consequently, a universally accepted management protocol is currently lacking and MDO-strategies vary across centers. In our center, considering our conservative approach, MDO is solely performed in patients with severe UAO or a tracheostomy tube that persists beyond infancy (>2 years). Furthermore, the obstruction needs to be found at the level of the tongue base, which is objectified by a Drug Induced Sleep endoscopy (DISE).

In **Chapter 5 & 6**, in view of the controversy on the MDO-procedure, our own surgical protocol is evaluated by focusing on the functional outcomes following MDO. According to the results among 22 non-isolated MH patients, MDO resulted in an improvement of the functional airway in the minority (41%) of our patients and UAO reoccurred in three (33%) of them. Six (27%) patients required a second MDO procedure in our center.

In **Chapter 5,** anatomical airway outcomes, as found by DISE, are presented. Although MDO seemed to be successful in lengthening the mandible in all patients, our results demonstrated that subsequent improvement of anatomical airway, as found by DISE, does not automatically imply that MDO is successful on the functional airway. Reasons for failed decannulation included the inability to intubate (high Cormack-Lehane score), resistance against capping the cannula, or an unsafe swallow function. Moreover, in six (27%) patients, improvement of the anatomical airway was not found at all, despite significant mandibular elongation. In these patients, MDO is very unlikely to be successful on the functional airway. Since DISE provides information on the site and nature of the airway obstruction and visualizes the effect of MDO, it can be of additional value in understanding the differences in functional airway outcomes after MDO and in this way might be helpful in optimizing treatment strategies. Hence, standardized use of DISE, in addition to the clinical assessment of mandibular position and a polysomnography, during MDO management is highly recommended.

In **Chapter 6**, feeding and swallowing function following MDO are examined. A high prevalence of feeding (82%) and swallowing difficulties (91%) was found in non-isolated MH patients that require MDO. These FD and SD often persisted after MDO (72% and 100%, respectively). The most important risk factors for persisting feeding and swallowing difficulties were found to be: pre-existing FD and SD and patients who are tracheostomy tube dependent. Another important finding was that feeding and swallowing function can (temporarily) aggravate after MDO. Awareness and close follow-up by a specialized multidisciplinary craniofacial team, including a specialized speech and language therapist, is of paramount importance in these patients.

In **Chapter 7**, the principal findings, in the context of the recent literature, of this thesis and subsequent limitations are discussed. Based on this knowledge, clinical recommendations are provided and future research perspectives are proposed.



Nederlandse samenvatting

CHAPTER 9.

Het doel van dit proefschrift is om een beter inzicht te krijgen in Robin Sequentie door te focussen op de klinische karakteristieken en de functionele uitkomsten na behandeling in ons centrum. Op deze manier proberen we waardevolle informatie toe te voegen aan huidige literatuur en hiermee trachten we bij te dragen aan het verbeteren van de zorg voor deze patiënten.

In **Hoofdstuk 1** wordt het onderwerp geïntroduceerd en de opbouw van dit proefschrift besproken. Tevens worden de huidige problemen in de literatuur belicht en de daarbij horende doelen van de thesis beschreven. Robin Sequentie (RS) is een aangeboren afwijking van het aangezicht die gekarakteriseerd wordt door een drietal van symptomen: mandibulaire hypoplasie, glossoptosis (terug liggende tong) en bovenste luchtwegobstructie. In ongeveer 90% van de patiënten is er ook een gespleten gehemelte aanwezig. Daarnaast presenteert ongeveer 80% zich met voedingsproblemen, welke gepaard kunnen gaan met slikproblematiek. RS kan geïsoleerd voorkomen (geïsoleerde RS), maar in de meerderheid van de gevallen komt het voor in combinatie met andere syndromen of aangeboren afwijkingen (niet-geïsoleerde RS). Naast dat het genotype (etiologie) erg kan verschillen, zit er ook een grote variabiliteit in de aanwezigheid en ernst van klinische symptomen. De combinatie van de grote heterogeniteit in zowel genotypen als fenotypen, die per patiënt significant kunnen verschillen, zetten clinici continu voor uitdagingen en maken de diagnose en behandeling complex.

Gezien mandibulaire hypoplasie (MH) het primaire kenmerk van RS is, kan het ophelderen van de rol van MH een goede stap zijn in het beter begrijpen van deze complexe aandoening. Om deze reden wilden we onderzoeken of het meten van mandibulaire lengte, naast de polysomnografie (PSG), van toegevoegde waarde is in de diagnose van RS. Op dit moment is er geen gouden standaard om MH te diagnosticeren. Hierdoor wordt de diagnose meestal klinisch (visueel) gesteld en is daardoor voornamelijk subjectief.

Hierop inspelend, wordt in **Hoofdstuk 2** een nieuwe, niet-invasieve, simpele en veilige meetmethode middels digitale fotografie gepresenteerd. Door mandibulaire lengte van RS-patiënten te vergelijken met “controle” patiënten, hebben we getracht meer duidelijkheid te creëren over de rol van MH in de diagnose van RS. Mandibulaire lengte werd verkregen doormiddel van de positie van de mandibula ten opzichte van de positie van het nasion te bepalen, welke werd gescoord als de Nasion-Mandibula Ratio (**NMRatio**). De resultaten van de studie onder 107 patiënten lieten zien dat de NMRatio, volgens de intraclass correlatiecoëfficiënt voor inter- en intraobserver variabiliteit (r=0.987 en r=0.808,

respectievelijk), een betrouwbare en reproduceerbare methode is om de lengte van de mandibula te meten. Echter werden er geen significante verschillen gevonden in de NMRatio tussen RS- patiënten en patiënten met alleen "klinisch gediagnosticeerde" MH, zonder luchtwegproblemen. Deze bevindingen wezen erop dat mandibulaire lengte, uitgedrukt in de NMRatio, in de eerste 3 levensmaanden geen sensitieve en specifieke voorspeller was voor de aanwezigheid en ernst van de luchtwegobstructie in kinderen met RS. Hierdoor kan mandibulaire lengte alleen gebruikt worden om clinici alert te maken voor mogelijke luchtweg problematiek in kinderen met een ogenschijnlijk kleine mandibula. Het uitvoeren van een PSG is echter noodzakelijk om de aanwezigheid en ernst van respiratoire problemen te diagnosticeren.

In de meeste patiënten verminderen de luchtweg problemen naarmate het kind ouder wordt, zonder dat er iets wordt gedaan (chirurgische interventie) aan de mandibula. Er wordt gesuggereerd dat dit zou komen door het fenomeen dat ook wel "mandibulaire inhaalgroei" wordt genoemd en zou specifiek aanwezig zijn in RS-patiënten. Echter blijft er tot op heden veel onduidelijk omtrent dit fenomeen. Om deze reden hebben we de groei van de mandibula gedurende de eerste 4 levensjaren bestudeerd. De resultaten in **Hoofdstuk 2** lieten zien dat de mandibula van RS patiënten niet dezelfde lengtes bereikten op de leeftijd van 4 jaar als die van "normale" kinderen van dezelfde leeftijd. Aan de hand van onze resultaten kon de aanwezigheid van deze "mandibulaire inhaalgroei", die specifiek bij RS patiënten op zou moeten treden, niet bevestigd worden.

Het volgende deel van dit proefschrift richt zich op de klinische uitkomsten na behandeling in ons centrum. Op dit moment is de behandeling van kinderen met RS controversieel en verschilt het behandelprotocol per centrum, afhankelijk van de voorkeur van dat centrum. Volgens het ethische principe: "do not further harm" volgen we in ons centrum een protocol waarbij we bij voorkeur kiezen voor een niet-chirurgische behandelingsoptie: de meeste kinderen met matig-ernstige OSA die niet direct een interventie (tracheotomie) nodig hebben worden behandeld met niet-chirurgische alternatieven (NPA, CPAP, zuurstof etc.). Op deze manier proberen we het aantal patiënten dat een chirurgische behandeling nodig heeft en de daarmee gepaard gaande comorbiditeiten te minimaliseren.

In **Hoofdstuk 3** worden de functionele uitkomsten na niet-chirurgische behandeling geëvalueerd. Deze studie onder 36 RS patiënten die gedurende het eerste levensjaar prospectief gevolgd en behandeld werden in ons centrum, liet een vrijwel volledige normalisatie van de respiratoire parameters zien. Vanaf het moment van start van de respiratoire behandeling (PSG1) tot stop van de respiratoire behandeling (PSG 2) tot aan de leeftijd van 1 jaar (PSG3), verminderde de obstructieve apneu hypopneu index van 7.0 naar 1.1 tot uiteindelijk 0.5. Daarnaast verdwenen gedurende dit eerste levensjaar de klinische symptomen van respiratoire problematiek, steeg het zuurstofgehalte in het bloed en verbeterden de capillaire bloedgas waarden naar zo goed als normaal. Dit suggereert dat nze niet-chirurgische behandeling succesvol lijkt te zijn op de luchtweg. Naast de luchtwegproblematiek, presenteerde een groot deel van de patiënten zich met voedingsproblematiek (86%). Ondanks dat de luchtwegobstructie behandeld werd, persisteerden de voedingsproblemen in 29% van de patiënten die zich presenteerden met voedingsproblematiek en 20% van de patiënten was nog steeds ondervoed op de leeftijd van 1 jaar. Daarnaast was de groei van deze patiënten ook zorgwekkend. Zowel gewicht naar leeftijd (WFA) en lengte naar leeftijd (HFA), uitgedrukt in de standaarddeviatie score (SDS), was aanzienlijk lager dan die van gezonde leeftijdsgenoten op de leeftijd van 1 jaar (-1.03 en -0.71, respectievelijk). Bovendien bleef gedurende het eerste levensjaar de SDS WFA verder dalen: van -0.40 tot -0.33 tot -1.03, voor respectievelijk PSG 1, PSG 2 en PSG 3. Deze bevindingen zijn zorgelijk en laten de urgentie van strikte evaluatie van voedingsproblemen en het monitoren van gewicht en lengte in RS patiënten zien.

In **Hoofdstuk 4** worden de functionele uitkomsten omtrent luchtweg, voeding en groei in 18 patiënten met Faciale Dysostosis (FaD) na behandeling in ons centrum beschreven. FaD is een zeldzame aangeboren afwijking van het aangezicht, veroorzaakt door abnormale ontwikkeling in de kieuwbogen tijdens de embryogenese. Onze resultaten lieten zien dat kinderen met FaD een verhoogd risico hebben op ernstige luchtwegobstructie (50%) en dat deze ernstige geobstrueerde kinderen vaak verminderde functionele uitkomsten hebben omtrent de luchtweg, voeding en groei. In ons centrum volgen wij een conservatief protocol en worden onze patiënten, waar mogelijk, niet-chirurgisch behandeld. Echter had het grootste deel van deze patiënten chirurgische interventie nodig (89%). Voedingsproblemen waren aanwezig in 72% en persisteerden in 54% van de patiënten met voedingsproblematiek. Slikproblemen waren aanwezig in 83% en persisteerden in 93% van de patiënten met slikproblemen. Op het eind van follow-up was nog steeds 25% van de patiënten ondervoed, ondanks het feit dat ze additionele sondevoeding kregen. Daarnaast bleek dat sluiting van het palatum een aanzienlijk risico geeft op het verergeren of terugkeren van de luchtwegobstructie,

ongeacht goede resultaten van de PSG met plaatje dat palatum sluiting simuleert. Noemenswaardig is dat twee patiënten zijn overleden tijdens follow- up. Concluderend blijkt uit onze resultaten dat FaD een complexe groep van patiënten met syndromale RS is die niet neigen te normaliseren over tijd. Hierdoor zijn de lange termijn uitkomsten in deze patiënten vaak ook matig. Om deze reden moeten zij gezien worden als unieke entiteit. Strikte follow-up bij een gespecialiseerd multidisciplinair team wordt sterk aanbevolen.

Het laatste deel van dit proefschrift beschrijft de functionele behandeluitkomsten na de mandibula distractie (MDO) in ons centrum. Ondanks dat er veel onderzoek is gedaan naar MDO, is er op dit moment geen consensus over indicaties voor chirurgie, de timing van chirurgie, en keuze voor chirurgische techniek door de verschillen in studie opzetten en heterogeniteit van studiepopulaties. Hierdoor ontbreekt een universeel geaccepteerd MDO-protocol en variëren de protocollen per centra. Gezien onze voorkeur voor een conservatieve behandelstrategie, wordt MDO in ons centrum pas uitgevoerd bij kinderen met persisterende luchtwegobstructie na de leeftijd van 2 jaar. Daarnaast moet bij deze kinderen een bewezen obstructie zitten ter hoogte van de tongbasis, welke gevisualiseerd wordt met behulp van een luchtweg scopie (DISE).

Gezien de controverse omtrent de MDO-procedure, evalueren we in **Hoofdstuk 5 & 6** van dit proefschrift ons eigen MDO-protocol door ons te focussen op de functionele uitkomsten na MDO. In negen (41%) van onze 22 niet-geïsoleerde patiënten resulteerde het verlengen van de onderkaak in een verbetering van de respiratoire problematiek, waarbij de luchtwegobstructie in drie van de negen (33%) patiënten nog wel een keer terugkwam. Zes (27%) patiënten ondergingen een tweede MDO in ons centrum.

In **Hoofdstuk 5** wordt, door middel van DISE beelden, gekekeken naar de anatomische luchtweg uitkomsten na MDO. Opvallend was dat verbetering van de anatomische luchtweg, zoals gezien werd bij de DISE, niet altijd resultuurde in het opheffen van, dan wel verbetering van, de functionele luchtwegobstructie. Dit kwam onder andere door de aanwezigheid van andere comorbiditeiten, zoals slikproblematiek, de onmogelijkheid om te decannuleren door een hoge Cormack-Lehane score, of dat het kind het afdoppen van de canule niet accepteerde. Merkwaardig was dat er in sommige patiënten helemaal geen verbetering van de anatomische luchtweg werd gezien, ondanks dat de mandibula substantieel verlengd werd. In deze patiënten is het erg onwaarschijnlijk dat de MDO succesvol gaat zijn op de functionele luchtweg.

Gezien DISE informatie geeft over de locatie(s) en ernst van de luchtwegobstructie en ook het effect van MDO op de luchtweg weergeeft, kan DISE van toegevoegde waarde zijn in het beter begrijpen van de luchtweg uitkomsten na MDO en het bepalen van behandelstrategieën. Om deze reden wordt de implementatie van het gestandaardiseerd uitvoeren van DISE tijdens het MDO protocol sterk aanbevolen.

In **Hoofdstuk 6** worden de voeding- en slikfunctie rondom de MDO onderzocht. In deze studie presenteerde een groot deel van de patiënten zich met voedingsproblematiek (82%) en slikproblematiek (91%). Daarnaast persisteerden zowel de voedings- als de slikproblemen in bijna alle patiënten (72% en 100%, respectievelijk). De belangrijkste risicofactoren voor het persisteren van de voeding- en slikproblemen waren pre-existerende voedings- en slikproblematiek en patiënten die een tracheotomie hebben. Een andere belangrijke bevinding was dat het eten en slikken (tijdelijk) kan verergeren tijdens of net na de MDO. Door middel van onze resultaten hopen we het bewustzijn van deze problematiek rondom MDO onder clinici te vergroten. Daarnaast is het van belang om bij deze patiënten nauw te volgen met een multidisciplinair team, met onder andere een gespecialiseerde logopedist.

In **Hoofdstuk 7** worden de belangrijkste bevindingen van de studies geanalyseerd en bediscussieerd. Tevens bevat dit hoofdstuk klinische aanbevelingen en worden nieuwe ideeën voor toekomstig onderzoek geopperd.

Appendices:

List of publications

PhD portfolio

Curriculum vitae

Dankwoord

CHAPTER 10.

List of publications

Functional outcomes in patients with facial dysostosis and severe upper airway obstruction

PPJM van der Plas, S Yang, M Streppel, B Pullens, SL Versnel, MJ Koudstaal, EB Wolvius, IMJ Mathijssen, KFM Joosten *Int J Oral Maxillofac Surg. 2021 Jul;50(7):915-923.*

Mandibular distraction to correct severe non-isolated mandibular hypoplasia: The role of drug- induced sleep endoscopy (DISE) in decision making

PPJM van der Plas, KFM Joosten, EB Wolvius, MJ Koudstaal, IMJ Mathijssen, MF van Dooren, B Pullens *Int J Pediatr Otorhinolaryngol. 2022 Jan;152:110968*

Can the Nasion-Mandibula Ratio Predict Obstructive Sleep Apnea in Patients With Retrognathia?

PPJM van der Plas, MJ Koudstaal, B Pullens, IMJ Mathijssen, EB Wolvius, KFM Joosten *FACE journal. 2022 Mar;3(1): 22 - 31*

Feeding and swallowing outcomes following mandibular distraction osteogenesis: an analysis of 22 non-isolated paediatric cases

PPJM van der Plas, M Streppel, B Pullens, MJ Koudstaal, IMJ Mathijssen, GGM van Heesch, EB Wolvius, KFM Joosten *Int J Oral Maxillofac Surg. 2022 Jul;51(7):892-899.*

Non-surgical respiratory management in relation to feeding and growth in patients with Robin sequence; a prospective longitudinal study*

PPJM van der Plas, GGM van Heesch, MJ Koudstaal, B Pullens, IMJ Mathijssen, SE Bernard , EB Wolvius, KFM Joosten **Under submission*

PhD Portfolio

Name PhD student:	Pleun van der Plas
PhD period:	September 2018 – February 2023
Erasmus MC department:	Oral- and Maxillofacial Surgery
Promotors:	Prof. dr. E.B. Wolvius Prof. dr. K.F.M. Joosten
Co-promotor:	Dr. M.J. Koudstaal

General Courses	**Year**
Scientific integrity course, Erasmus University Medical Center, Rotterdam	2019
Basiscursus Regelgeving en Organisatie (BROK), Erasmus University Medical Center, Rotterdam	2019
CPO research day Erasmus University Medical Center, Rotterdam	2019
Biomedical English writing and communication course, Erasmus University Medical Center, Rotterdam	2019

Specific Courses	
Scoren van respiratoire slaap events, Sleep vision, Nijmegen	2018
PubMed course, Erasmus University Medical Center, Rotterdam	2018
Limesurvey course, Erasmus University Medical Center, Rotterdam	2018
Gemstracker course, Erasmus University Medical Center, Rotterdam	2018
OpenClinica course Erasmus University Medical Center, Rotterdam	2018
Endnote course, Erasmus University Medical Center, Rotterdam	2020
NIHES: Practice of Epidemiologic Analysis (ESP65)	2020
NIHES: Quality of Life Measurement (HS11)	2020
NIHES: Principles of Research in Medicine and Epidemiology (ESP01)	2021
NIHES: Fundamentals of Medical Decision Making (ESP70)	2021

Seminars and workshops

PhD day	2018 2019
EARP – Erasmus MC Anatomy Research Project: upper extremity	2019

Other

Writing BOOA Research grant	2020

Presentations	**Year**
NVSCA Najaars congres	2019
ICK-research meeting	2020
Cranio refereer avond	2020
ICK-research meeting	2021
EACMFS MDO-DISE	2021
EACMFS MDO- FD&SD	2021
OAMFS-research meeting EMC	2021
Landelijke kinder-CTB refereer avond	2021
EIP conference– NMRatio	2021
ESCFS Oxford	2022

(Inter)national conferences

ECPCA congress Utrecht	2019
NVSCA Najaarscongress Groningen	2019
NVMKA Najaarscongres (Online)	2020
EACMFS Paris (Online)	2021
EIP Amsterdam (Online)	2021
ESCFS Oxford	2022

Curriculum vitae

Pleun van der Plas was born on March 28th 1995 in Oosterhout (NB), the Netherlands. She graduated from the Mgr. Frencken college in Oosterhout (NB) in 2013. In the meantime, she was selected for the junior national field hockey teams (U16, U18) for which she played several international tournaments and won 2 times European gold (2010, 2013). Directly after she finished high school, she started her study Medicine at the medical faculty of the Erasmus Medical Center. During her bachelor Medicine, she was selected for the national field hockey team U21, for which she won a European Cup golden medal (2014) and a World Cup silver medal (2016). From the age of 21 onwards, she started playing at hockey club Den Bosch (Dames 1) which she combined with her study with great pleasure. During these six years, she won both the national championship (4 times) and the European Championship for club teams (3 times). After finishing her bachelor degree in 2017, she started her master thesis under the supervision of Robbin de Goederen, who created the special interest for patients with Robin Sequence. During writing her master thesis, the enthusiasm and passion for this patient population was further expanded. After finishing her master thesis, she was given the opportunity to start her research trajectory on Robin Sequence as a PhD student under the supervison of Prof. dr. Eppo Wolvius, Prof. dr. Koen Joosten, and dr. Maarten Koudstaal. Simultaneously, she completed the Erasmus Anatomy Research Project (EARP) on the upper extremity. During the last year of her PhD, she was selected for the Dutch National team, for which she played her first international caps. Currently, besides playing hockey, she has started a job at BDO as a junior advisor on strategy & organization in the healthcare sector. In the meantime she is awaiting to start with her internship to finish her master's degree in pursuit to fulfill her dream of becoming an Oral- and Maxillofacial surgeon.

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Dankwoord

Alone we can do so little, together we can do so much – Helen Keller

Het uitgevoerde onderzoek met als resultaat dit proefschrift is een gezamenlijke inspanning geweest. Om deze reden wil ik dan ook iedereen die een bijdrage heeft geleverd aan dit proefschrift bedanken. Zonder iemand tekort te doen, wil ik hier een aantal mensen in het bijzonder bedanken.

Allereerst alle patiënten en hun ouders die hebben meegewerkt aan dit onderzoek. Zonder jullie had ik dit promotie onderzoek niet kunnen verwezenlijken. Mijn dank is groot!

Mijn promotoren Prof. dr. Eppo B. Wolvius & Prof. dr. Koen F.M. Joosten; en mijn copromotor Dr. Maarten J. Koudstaal, ik wil jullie onwijs bedanken voor de kans die ik heb gekregen om dit onderzoek uit te mogen voeren. De ruimte die jullie mij hebben gegeven rondom mijn sport en de support die ik van jullie heb ontvangen, hebben mij door dit hele traject gesleept. Zonder jullie hulp, vertrouwen en steun was het zeker niet gelukt! Ik voel me bevoorrecht om met jullie te hebben mogen samenwerken! Eppo, bij jou staat kwaliteit voorop en met jouw aandachtige blik en kritische vragen kwam jij altijd binnen een mum van tijd tot de kern van de vraag. Jouw scherpe commentaren en de snelheid waarmee je deze gaf (zondag avond 23u of maandag ochtend 6u) hebben dit proefschrift naar een hoger niveau getild en zorgden ervoor dat ik er ook altijd naar heb gestreefd het beste bij jullie aan te leveren, waar kon, zo snel mogelijk. Ik bewonder de manier waarop jij betrokken bent en blijft bij het onderzoek en je onderzoekers/ medewerkers, altijd bezig bent met het leveren van de beste zorg voor je patiënten (dan wel deze te verbeteren) en daarnaast ook nog eens de afdeling runt! (Mede) door jou is mijn passie voor de kaakchirurgie de afgelopen jaren alleen maar verder toegenomen! Dank!
Koen, de drijvende kracht achter het schrijven van dit proefschrift. Jij was de coördinator van dit project en zorgde met jouw onuitputtelijke inzet ervoor dat ik ook altijd nog 1 stapje extra wilde zetten om het beste uit mezelf te halen! Je gaf me het gevoel dat je deur altijd open stond, ook wanneer ik even door de bomen het bos niet meer zag. Onwijs veel dank hiervoor! In het begin als copromotor maar na een jaar mocht ik jou dan ook officieel mijn promotor noemen. Deze prestatie is ook uitzonderlijk en wil ik niet aan me voorbij laten gaan. Desondanks veranderde er eigenlijk weinig in onze samenwerking: nog steeds was jij toegankelijk, behulpzaam en begripvol. Daarnaast heb ik jouw toewijding voor de (ic) kinderen altijd bewonderd en deze hebben mij dan ook echt geïnspireerd: zo wil ik later ook zijn/ worden als arts. Maarten, na een jaar werd jij aan ons “team” gevoegd en konden we aan de bak! Je enthousiasme voor het vak kaakchirurgie en je inzet voor zowel de patiënten als het onderzoek zijn aanstekelijk. Je kritische, maar verfrissende blik en je innovatieve ideeën voor

onderzoek daagden mij altijd uit om nog net wat verder te kijken, te denken en te onderzoeken! Dank voor deze inspirerende en wijze lessen!

Geachte leden van de leescommissie: Prof. dr. Benninga, Prof. dr. Mink van der Molen en Dr. Duijts, hartelijk dank voor jullie bereidheid dit proefschrift op zijn wetenschappelijke waarde te beoordelen. Jullie kennis vanuit diverse achtergronden geeft wetenschappelijke verdieping aan de commissie.
Geachte leden van de grote commissie, hierbij wil ik jullie ook alvast hartelijk danken voor de bereidheid om mijn proefschrift te lezen. Ik zie uit naar de gedachtewisseling.

Beste dr. Pullens, beste Bas, ik heb je leren kennen op de LTS-poli als iemand met een open karakter, nuchtere blik en veel humor (en iemand die erg van koekjes houdt ;)). Ongeveer een jaar later kwamen we ook op onderzoeksgebied samen door de gedeelde interesse in de luchtweg (scopie) uitkomsten van kinderen die een mandibula distractie hebben ondergaan. Door naar deze hele specifieke groep patiënten te kijken, kwamen we achter interessante uitkomsten die de nodige vervolgvragen opriepen. Daarnaast wil ik je ook onwijs bedanken voor de prettige samenwerking!

Beste drs. Gwen, jouw kennis en feeling voor de ic-kinderen heeft de kwaliteit van dit onderzoek verhoogd. Dank voor jouw opmerkzame blik, je kritische vragen en scherpe revisies. Dank voor het sparren en de kwalitatieve samenwerking! Veel succes met het vervolgonderzoek!

Beste drs. Streppel, beste Marloes, de samenwerking met jou als logopedist en daarbij de achtergrond van de onderliggende slikproblematiek bij deze kinderen is een grote toevoeging geweest voor dit proefschrift. Diverse malen bracht jouw deskundige blik goede inzichten naar voren, die hopelijk de zorg voor deze patiënten in de toekomst gaat verbeteren! Veel dank voor je input en de fijne samenwerking!

Alle medeauteurs, dank voor jullie waardevolle input! Zonder jullie was dit proefschrift niet tot stand gekomen.

Lieve Sumin, mijn PhD maatje, mijn steun en toeverlaat! Wat ben ik blij dat wij elkaar hadden! (Bijna) tegelijkertijd begonnen en samen hebben wij heel wat uurtjes op de 15e gespendeerd. Jouw (statistische) kennis en jouw gedrevenheid en perfectionisme hebben mij altijd getriggerd om tot de beste versie te komen. Samen hebben wij door alle fasen van de PhD gelopen en hier heb jij mij dan altijd door heen geholpen, ook wanneer het een keer wat lastiger was! Dank voor alle mentale support, het sparren en de peptalks. Nog heel even geduld en dan kan ook jij je proefschrift gaan verdedigen.

Beste dr. De Goederen, beste Robbin, tijdens mijn masteronderzoek wist jij mijn interesse te wekken voor kinderen met Robin Sequentie en het doen van onderzoek. Je motiverende gesprekken en leerzame correcties hebben mij onwijs geholpen om tot een eerste (vorm van) manuscript te komen. Ik wil je onwijs bedanken voor de hulp (inclusief tips) die je in deze periode, waarin ik kennis mocht maken met het wetenschappelijk onderzoek, hebt geboden!

Joke, de (stille) motor achter het onderzoek van de kindergeneeskunde. Als rechterhand van Koen help je iedereen met een vraag over onderzoek. De rust die je uitstraalt gaf me vertrouwen om alle stappen van het doen van onderzoek (samen) te doorlopen! Dankjewel voor al je hulp!

Mariska, Jacoba, Elin, Mirjam, onwijs veel dank voor jullie bijdrage aan de zorg voor de cranio/luchtweg patiënten en jullie gezelligheid (op de poli)! Karolijn, dank voor je waardevolle input over QOL omtrent (RS) patiënten en de plezierige samenwerking!

Collega's van de 15e; Joris, Saranda, Sumin, Lisa, Melissa, Romy, Nine, Linda, Robbin, Bianca, Mark, Ralph, Jaap, Thijs, Stephanie, Xavier, Babette en Alex, dank jullie wel voor een geweldige tijd! Met name de gezamenlijke koffie momenten, de gezellige borrels en de maandelijkse sterren lunch hebben mijn tijd op de 15e onvergetelijk gemaakt. Helaas kon dat het laatste deel van mijn promotie traject een stuk minder vanwege Corona, maar dat heeft me des te meer doen beseffen hoe leuk het was om met jullie daar samen te werken! Nogmaals dank en succes allen met de aankomende stappen!

Nienke en Iris, onze tijd als masterstudenten op de 15e is me altijd bijgebleven. Door onze gezamenlijke interesses en gedeelde humor was het altijd leuk om naar "studie" te komen. Laten we de 15e meetings er vooral in houden!

Paranimfen Frederieke en Jeske, wat fijn dat jullie naast mij staan tijdens de promotie. Jes, ondanks dat we elkaar nog niet zo lang kennen, voelt het alsof je er altijd al bent geweest. In een korte tijd ben je zo belangrijk voor me geworden! Lieve Fré, bij jou juist het tegenovergestelde: ik heb het geluk dat ik jou al mijn hele leven naast me heb! Zoals mama altijd zegt: wij zijn er altijd voor elkaar!

Marieke (vG) & Sjoerd, vanaf de luiers aan de kant van het hockeyveld en hopelijk tot aan in de rollator! Wat hebben wij al veel meegemaakt samen! Het is altijd een feestje met jullie: ik ben nog nooit met jullie geweest, zonder weg te gaan met pijn in mijn buik van het lachen. Daarnaast voelen jullie ook echt als familie! Ik hoop dat we deze speciale band nog heel lang mogen voortzetten, hier en/of in Griekenland!

Eefje en Floor, ik ben zo dankbaar voor onze vriendschap! Uit het oog is zeker niet uit het hart want onze fijne jaren in Den Bosch met de brunches bij de YB op zaterdag ochtend hebben een band geschept die nooit meer weg zal gaan! Ik weet dat we er altijd voor elkaar zijn, in goede, maar ook in de wat moeilijkere tijden!

Laura (vH), Fabienne, Emmeliene, Sanne, Laura (N), Sian, Frederique, Imme en Pien, buiten hockey ook hele dikke vriendinnen geworden! Het is zo ontzettend bijzonder om alle mooie herinneringen die we gemaakt hebben met hockey samen met je vriendinnen te kunnen delen. Inmiddels gaan we langzaam maar zeker allemaal onze eigen weg: de een gestopt (vanwege maatschappelijke ambities), de ander nog volle bak in de richting van Parijs 2024. Ik ben blij dat ik eenieder van jullie linksom of rechtsom om me heen heb en hoop nog heel veel tijd (en vakanties) met jullie samen te delen!

Floor, Merel (B), Karlijn, Floor Denice, Emilie, Nathalie en Maxime, we go waaaay back: als jonge pubers op het Frencken College tot nu! De vriendschap die we in die tijd hebben opgebouwd is mij zo waardevol en blijft voor het leven!

Brit, Judith (Q), Merel (A), Fee, Roos, Sophie en Marieke (B), tijdens onze gouden jaren bij Push hebben we een super fijne vriendschap opgebouwd. Naast onze gedeelde passie voor hockey, kon ik ook alles met jullie delen op sociaal en maatschappelijk gebied, want er was niemand die dat zo goed begreep als jullie! Ik ben heel erg blij met jullie en zie uit naar al onze gezellige (steden)tripjes/ vakanties die nog komen gaan!

Fleur, Kirsten en Annette, ons huisje op de Statenweg was altijd zo fijn! We hebben er een aantal intense jaren doorgebracht tijdens Corona, met thuis werken, quarantaines en dakterras (sport)sessies. De huisavondjes (met karaoke) zijn goud waard en wat ben ik blij met onze vriendschap! Deze is mij altijd enorm waardevol!

Eva, Lisa, en Judith (M), ons fijne huisje op de Lekstraat voelt echt als thuis! Ik ben iedere keer blij wanneer ik weer thuis kom (met een bak popcorn op de bank;)). Naast de huisavondjes, geniet ik ook enorm van de gezellige huis etentjes, borrels en stap avondjes. Ik hoop deze nog lang samen met jullie te mogen delen!

HC Den Bosch toppers, van al mijn hockey jaren heb ik het langst met jullie mogen spelen. En wat voor een team! Ik ben zo blij en trots dat ik onderdeel mag uitmaken van dit bijzondere en fantastische team! Wat heb ik veel van jullie en de “Bossche mentaliteit” geleerd. “Geel zwart, dat draag je met je hart!”

Mijn lieve familie: opa Leo, oma Annie, oma Nel, Johan, Fred, Marja, Anne, Karlijn, Noud, Mitch en Loeiki, ik ben zo dankbaar dat ik zon lieve en fijne familie om me heen heb! Ondanks dat ik niet altijd bij onze familie uitjes en wintersportreisjes kon zijn, waren jullie mijn trouwste supporters. Wanneer ik jullie nodig had, waren jullie er altijd voor mij. Dankjewel!

Lieve Koen en Féline, wat ben ik blij dat jullie aan onze familie zijn toegevoegd! Koen het is altijd een feestje als je bij ons (of ik bij jullie) bent! Daarnaast ben ik zo blij om te zien dat je Fré zo gelukkig maakt! Met de komst van de lieve Féline is dat geluk alleen maar toegenomen! Lieve Féline, we kennen elkaar nu bijna een jaar en mijn liefde voor jou is nu al zo ontzettend groot! Ik ben een enorm trotse tante!

Lieve Frederieke en Jip, ik denk dat ik niet in woorden uit kan drukken hoe blij ik met jullie ben en hoeveel ik van jullie hou. Jullie hebben mij altijd gesteund in mijn 2 passies. Ik ben jullie zo dankbaar dat jullie me altijd de ruimte hebben gegund die ik daar voor nodig had. Jullie zijn de beste broer en zus die ik me maar kan wensen en ik ben zo zo zo trots dat ik jullie zus(je) mag zijn! Weet dat ik er ook altijd voor jullie ben en jullie steun in alles wat jullie doen! Fre, de liefste en meest betrouwbare persoon op deze aardbol. Jij bent mijn voorbeeld in hoe je naar de mensen om je heen wil zijn: lief, betrouwbaar en loyaal. Door haar persoonlijkheid omringd door zoveel liefde en lieve mensen! Jip, mijn misschien stille, maar o zo belangrijke sparringpartner. Geen open boek, maar wanneer je iets zegt, sla je de spijker op zijn kop! Altijd sta je voor anderen klaar, oprecht een hart van goud! Ik hou van jullie!

Lieve pap en mam, jullie van iedereen het meest bedankt! Dank voor jullie onvoorwaardelijke liefde en steun bij alles wat ik doe! Jullie stimuleren, motiveren en inspireren mij om altijd het beste uit mezelf te halen! Door jullie vind ik kracht om dat te blijven doen, wat er ook gebeurt. Ik voel me bevoorrecht dat ik samen met Fré en Jip heb mogen opgroeien in zo'n fijne omgeving waar we alle kansen en mogelijkheden heb gekregen om te worden wie we nu zijn. Jullie hebben ons geleerd om niks voor lief te nemen en dat wanneer je iets wil bereiken, je daar zelf hard voor zult moeten werken. Dank voor deze wijze levensles(sen).Lieve pap, mijn grote tegenpool, jij die altijd je rust weet te bewaren, wat mij soms alleen maar verder de kast op jaagt. Desalniettemin ben je er altijd voor mij/ons en zoals ze zeggen: "actions speak louder than words". Lieve mam, ze zeggen vaak dat ik op jou (en opa) lijk. Ik ben het daar niet altijd mee eens, maar 1 ding weet ik heel zeker: als ik van iemand doorzettingsvermogen en fanatisme heb meegekregen, dan is dat van jou! Dankjewel voor al je (ongevraagde) adviezen en levenslessen, dankjewel dat je altijd het beste voor me wil! Ik laat het soms niet genoeg merken, maar waardeer dat enorm. Ik hou onwijs veel van jullie!