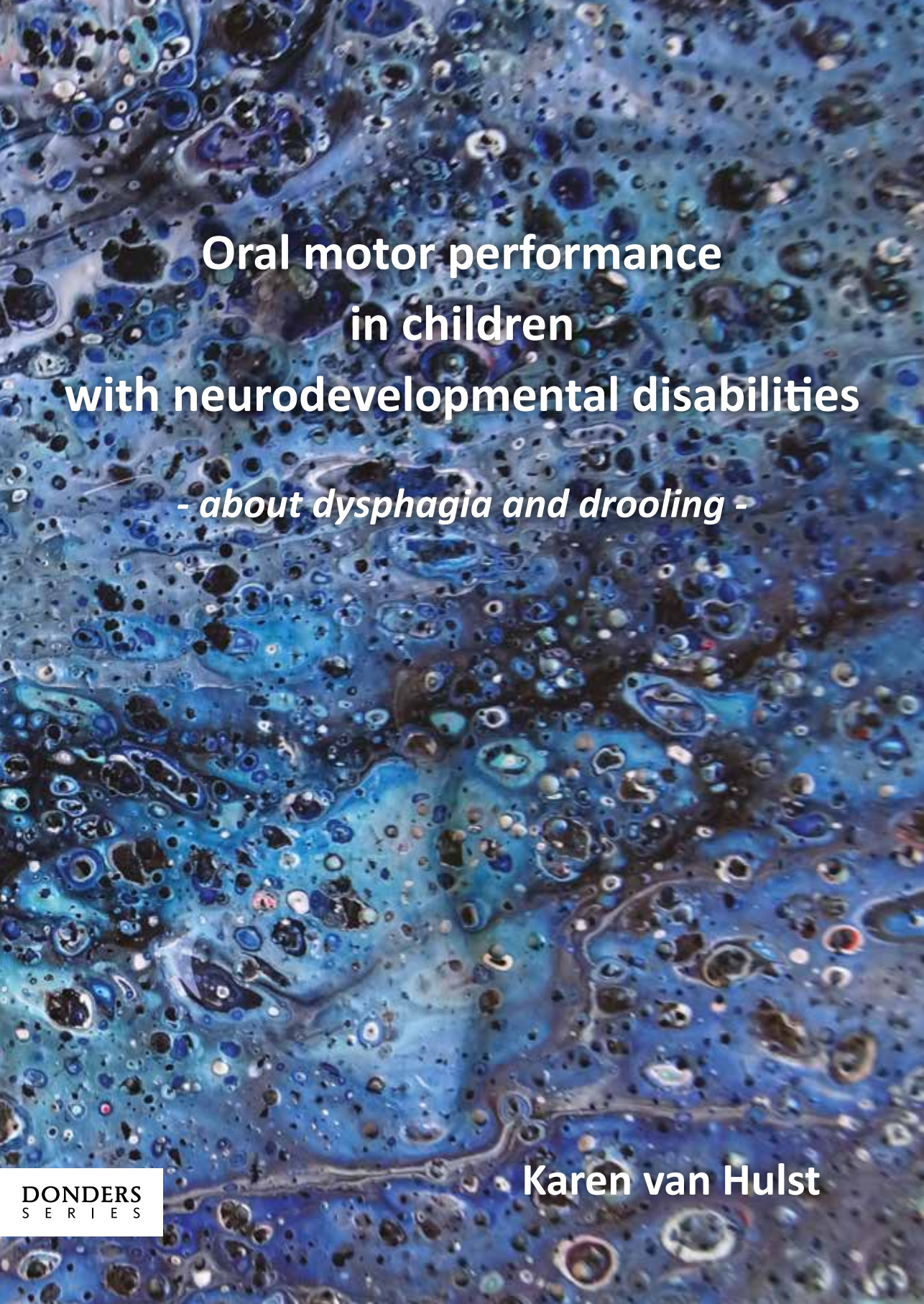

Oral motor performance in children with neurodevelopmental disabilities

- about dysphagia and drooling -

Karen van Hulst

DONDERS SERIES

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Promotor:
Prof. dr. A.C.H. Geurts

Copromotoren:
Dr. C.E. Erasmus
Dr. P.H. Jongerius (Sint Maartenskliniek, Nijmegen)

Manuscriptcommissie:
Prof. dr. C. Noordam
Prof. dr. B. Steenbergen
Prof. dr. R.J. Vermeulen (Maastricht UMC)

Vol liefde opgedragen aan mijn ouders

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1

CHAPTER 1

General introduction

Oral motor performance

Oral motor performance refers to the daily-life execution of oral motor tasks in a person's natural environment. This thesis focuses on complex oral motor activities in seriously impaired children: eating and drinking, swallowing, and saliva control.

In normal circumstances, eating and drinking are daily activities that guarantee sufficient food and liquid intake, but also create opportunities for children and their caregivers to communicate and socially interact, which forms a basis for normal development.[1] However, in children with neurodevelopmental disabilities, e.g. due to cerebral palsy (CP), it may be challenging to eat, drink, swallow, and control saliva in an efficient and safe way, which jeopardizes their intake and social development. Quite often, oral motor problems in these children are associated with other CP-related conditions such as epilepsy, cognitive impairments, behavioral problems, and/or perception and sensation disorders. Furthermore, possible impairments of the oral region show a large variation and complex association with other sensorimotor impairments, leading to diminished oral motor performance. For example, difficulties with swallowing can be associated with excessive drooling,[2] and difficulties with eating and drinking can arise when intake is disturbed by poor gross motor function or intellectual impairment.[3]

The limited oral motor performance in children with neurodevelopmental disabilities inevitably results in feeding difficulties caused by the interaction of (1) dysfunctional oral motor control (weak sucking, persistent tongue protrusion or thrusting, poor lip closure, poor bolus formation), (2) abnormal neurological maturation (presence of oral pathological reflexes like biting, gagging), and (3) low level of motor ability and poor seating posture during feeding.[4] In the child with neurodevelopmental disability, body posture and the sequence of essential oral events may be compromised by abnormal tone and movement patterns. It is important to secure correct postural alignment in order to achieve safe swallowing and sufficient feeding. Effective oral functioning for feeding begins with attaining head stability to ensure jaw control. Head stability, however, is influenced by trunk alignment, which in turn is dependent on the stability of the pelvic area.[5]

Besides the oral motor problems, the feeding process can be disrupted by gastro-intestinal problems like gastroesophageal reflux, vomiting, constipation, and dysmotility disorders.[6] In addition, children with neurodevelopmental disabilities have difficulties expressing themselves because of speech problems or cognitive impairments. In this respect, it can be hard for the child to make clear to the environment his/her food preference or the need of food and liquid in the first place. Side effects of medication can also have a serious impact. For example, spasmolytic, anticholinergic and anti-epileptic drugs may affect appetite and/or gastrointestinal motility.[7]

Due to the complexity of these children, organized care during their development is needed. For this reason, since 2000, forces have been joined at the Radboud university medical center by forming an interdisciplinary, outpatient saliva control and swallowing team. Over the past two decades, hundreds of children have been referred to this team. The team includes a pediatric neurologist, an ear-nose-throat (ENT) specialist, a pediatric rehabilitation specialist, a psychologist, and speech-language therapists (SLTs). Parents are part of the team as the primary caregivers and decision makers of their child. There is collaboration 'on demand' with other disciplines such as dentistry, gastroenterology, pediatrics, dietetics, physiotherapy, and occupational therapy. In addition, the department of radiology can perform video fluoroscopic swallow studies (VFSS). The team members are armed with knowledge about the (patho)physiology of swallowing and are experienced in assessing and treating dysphagia and drooling. A well structured approach to diagnosis and treatment is followed and children are consistently monitored before and after any (proposed) intervention. The outcomes of all measurements are registered in a database. The mission of the team is to improve health-related quality of life in children with neurodevelopmental disabilities and their caregivers and to enhance meaningful participation in everyday life. SLTs take care of accurate assessment of eating and drinking abilities and advise about long-term treatment of dysphagia and drooling. As the nature of eating, drinking and swallowing problems is multifactorial, all levels of the international classification of functioning, disability and health: children and youth version (ICF-CY)[8] (i.e., impairments, activity limitations, participation restrictions) are addressed in a comprehensive assessment. Not only 'capacity', describing what a child is able to do in an optimal situation, but also 'performance', representing what a child actually does in his/her natural environment, are assessed. Despite the apparent increase in the number of children with feeding and swallowing disorders, validated classification systems, assessment tools, and outcome measures are largely lacking.[1] These gaps in the clinical work-up of assessing oral motor performance and managing dysphagia and drooling form the inspiration for this thesis.

Dysphagia

The term dysphagia is derived from Greek and means 'problematic'(dys) – eating (phagein). It refers to problems in any or all of the four phases of swallowing. Swallowing is a complex process during which saliva, liquid, and (chewed) food are transported from the mouth into the stomach while keeping the airway protected.[9] For safe feeding and swallowing the integrity of five nerves and more than 30 muscles is needed to make voluntary movements and generate effective oral and pharyngeal reflexes.[10] The 'oral preparatory phase' is initiated when food is taken into the mouth to process it and mix it with saliva to form a bolus. The 'oral transit phase' consists of the posterior propulsion of the bolus through the oral cavity, whereby jaw-closing muscles stabilize the mandible in a closed position. The 'pharyngeal phase' begins when the swallowing reflex is triggered and has two crucial biological features: (1) food passage, propelling the food through the pharynx and upper

esophageal sphincter (UES), and (2) airway protection, insulating the larynx and trachea from the pharynx during passage of food or saliva to prevent aspiration.[10] The 'esophageal phase' starts with relaxation of the UES during a swallow and allows the bolus passage through the esophagus to the stomach.

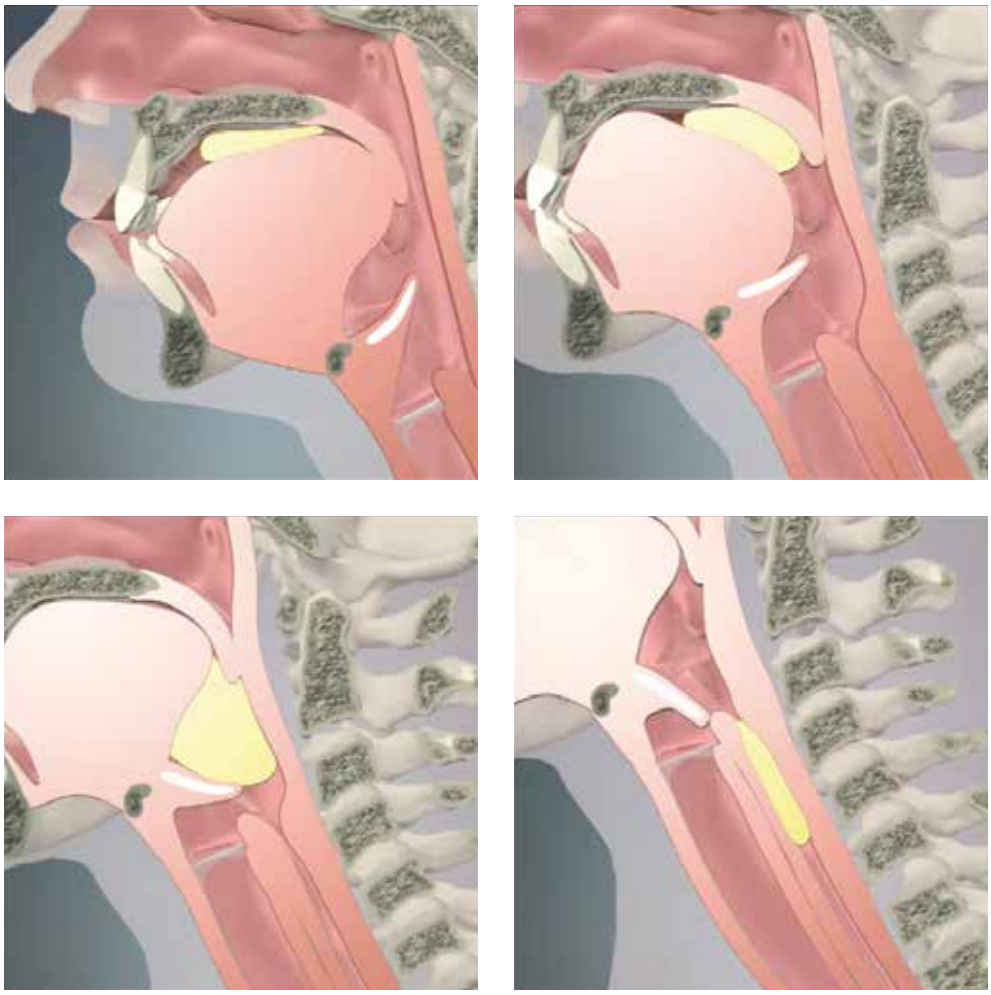

Figure 1. Phases of the swallowing process

In pathologic conditions three syndromes of chronic pulmonary aspiration have been described: aspiration of toxic contents (i.e. gastric acid); aspiration of pathogenic bacteria transmitted by saliva; and aspiration of inert substances.[11] Chronic aspiration of saliva is the least common form of aspiration and is often not diagnosed prior to the development of lung injury. Aspiration can be caused by swallowing dysfunction, anatomic or dynamic abnormalities of the airways, and/or circumstances that overrule the child's capacity to protect the airway (for example during vomiting).[12]

The estimated international prevalence of pediatric dysphagia in patients with neurodevelopmental disabilities ranges from 27 to 99%. These prevalence estimates should be viewed with caution since they depend on the description of the feeding difficulties or dysphagia, the characteristics of the study population, and the diagnostic instruments selected.[3, 13-15] The rate of newly diagnosed cases of pediatric dysphagia is unknown but there is general agreement that the occurrence of feeding and swallowing dysfunction is increasing, probably because of the improved survival rates of premature born children and children with complex medical conditions.[16] In children with CP or other neurodevelopmental disabilities, oropharyngeal dysphagia is a major risk factor for morbidity and mortality.[17] It leads to the inability to safely consume sufficient food and liquid and is associated with prolonged mealtimes, poor growth and malnutrition, and with respiratory consequences due to oropharyngeal aspiration.[18] These swallowing problems cause a significant distress to affected children and their caregivers and have a great impact on the health and well being of the children and their families.[19] In a study of children with severe CP (severe mobility problems, wheelchair depended) and intellectual disability (IQ<55)) parents tended to underestimate the severity of dysphagia probably due to habituation or low expectations of the feeding performance of their child.[15]

Feeding is the process that involves all aspects of eating and drinking, including gathering and preparing food and liquid for intake, sucking and chewing, and swallowing.[9] A feeding disorder is identified when a child is unable or refuses to eat or drink a sufficient quantity or variety of food to maintain proper nutrition. To get a grip on identifying feeding and swallowing difficulties, Arvedson proposed four key questions to assist parents in identifying children who require comprehensive evaluation.[20] These questions cover mealtime duration, mealtime stress, and concerns about growth and respiratory conditions with corresponding indicators for referral ('red flags'). The answers help determine if a comprehensive clinical feeding and swallowing assessment is needed, even though the answers do not necessarily define the problem.

1. *How long do mealtimes typically take?* If more than about 30 minutes on any regular basis, there is a problem. Prolonged feeding times are major red flags pointing to the need for further investigation.
2. *Are mealtimes stressful to the child or the parent?* Regardless of factors that underlie the stress, further investigation is needed. It is very common for parents to state that they "just dread mealtimes".
3. *Does the child show any signs of respiratory stress?* Red flags may include rapid breathing, gurgling voice quality, nasal congestion that increases as the meal progresses, or respiratory illness.
4. *Has the child gained insufficient weight in the past 2 to 3 months?* In the first 2 years of life, steady and sufficient weight gain is particularly important for brain development and general growth. A lack of weight gain in a young child is a red flag, like weight loss in an older child or adult.

Comparable to Arvedson, Benfer[21] proposed two questions (*Does your child have difficulty eating?* and *Does your child have difficulty drinking?*), which are scored on a Visual Analogue Scale (VAS), to detect children with feeding and swallowing difficulties and malnutrition. Both methods may be valuable to improve adequate and timely referral to an SLT.

The clinical evaluation of a child with neurodevelopmental disabilities related to feeding and swallowing includes a thorough history, physical examination, and feeding observation. Instrumental assessments of swallowing may be needed when there are concerns regarding pharyngeal phase physiology and increased risk of aspiration during oral feeding. A VFSS is the preferred method to evaluate the swallowing process, as it allows visualization of all phases of swallowing. In this way, different patterns of dysphagia can be determined in children with central and peripheral neurological disorders.[22] Unfortunately, there are only few validated observation instruments to assess eating and drinking problems in children with neurodevelopmental disabilities. Benfer et al.[23] evaluated nine oral-pharyngeal observation instruments and concluded that only two instruments (Schedule for Oral Motor Assessment (SOMA)[24] and Functional Feeding Assessment modified[25] (FFAm)) had good psychometric properties. Regrettably, there are no Dutch versions of these instruments available. Only the Dysphagia Disorder Survey (DDS)[26], the Mastication Observation and Evaluation (MOE)[27], and the 6-min mastication test (6 MMT)[28, 29] are available in Dutch. Recently, the Test of Masticating and Swallowing Solids in Children (TOMASS-C)[30] has been developed as a quantitative assessment of discrete oral stage components of solid bolus ingestion. The TOMASS-C has (internationally) proven to be a reliable diagnostic tool in preschoolers up to young adults that are able to follow instructions. To classify the functional performance, Sellers et al.[31] developed a valid and reliable functional eating and drinking ability classification system (EDACS) for children with CP as an addition to already existing functional CP classification systems for general movement[32, 33], manual ability[34] and communication.[35] However, a reliable Dutch classification system for eating and drinking abilities in children with CP is lacking. We, therefore, aimed to assess the reliability and validity of the translated EDACS in Dutch children with CP (chapter 4).

After adequate assessment, the ultimate goal of feeding and swallowing interventions is to provide the child with a stable airway, and with adequate nutrition and hydration during a safe, pleasant and relaxed mealtime. Because there is a growing awareness among clinicians that, already in early stages, particular attention should be paid to the importance of dysphagia, we considered it useful to write a review with recommendations for the assessment and treatment of dysfunctional swallowing in children with CP (chapter 3).

Drooling

Drooling or lack of saliva control is a normal phenomenon in the growing child, although it is unknown up to what age and to what extent drooling occurs in healthy children. For this reason, the development of saliva control was investigated in healthy children (normal

development, age 0 – 4 years) (chapter 2). In children with neurodevelopmental disabilities, drooling may persist due to a swallowing disorder in the oral and/or oral-pharyngeal phase. Hypersalivation is not considered to be a significant cause of drooling in children with CP, however, there may be arguments for increased salivary flow in children particular with dyskinetic CP.[36] By far the largest saliva production in humans comes from the paired parotid, submandibular and sublingual glands. The submandibular glands are responsible for the production of approximately 65-70% of all saliva in rest.[37] The parotid glands are mainly active following tactile or gustatory stimulation. At rest, they are responsible for about 20% of all saliva but, when stimulated, this may well amount to over 50%.

From a clinical point of view, it makes sense to distinguish between 'anterior' and 'posterior' drooling.[6] 'Anterior drooling' is the visible consequence of lack of oromotor control and refers to unintentional loss of saliva from the mouth. 'Posterior drooling' refers to saliva that is spilled over the tongue through the faucial isthmus. Normally, the sensation of saliva in the hypopharynx initiates a swallowing reflex. However, when the trigger to swallow is impaired or missing, pooled saliva may lead to posterior drooling, which may lead to alarming congested breathing, coughing, gagging, vomiting and at times saliva aspiration into the trachea.[38] Up to 78% of the children with neurodevelopmental disabilities may have complaints of anterior drooling, with a mean prevalence of about 40%.[3, 13, 14, 39] The prevalence of posterior drooling is unknown, but estimated to be 10-15% in the population with severe neurodevelopmental disabilities. Drooling negatively affects physical health and well-being and also has an adverse effect on social and emotional functioning.[40, 41] To understand the multifactorial nature and impact of drooling, it is important to assess underlying factors and to evaluate the effects of treatment. A combination of measures is often recommended focusing on modifying (1) underlying factors of drooling, (2) severity and frequency of drooling,[42, 43] and (3) impact of drooling on the child and family.[40, 44] The severity of drooling can be quantified by a range of objective and subjective measures. Objective measures include the salivary flow rate and the drooling quotient (DQ),[43] which are assessed by the SLT. To develop a more accurate and time-efficient instrument we reassessed the time span of the existing drooling quotient (chapter 5). Subjective scales include the Drooling Severity and Frequency Scale (DSFS),[42] the Teacher Drool Scale (TDS),[45] a parent questionnaire to assess the impact of drooling, and scaling the severity by a Visual Analogue Scale (VAS);[41, 46] scales that are mostly rated by the children themselves, their parents or caregivers. Despite all these available outcome measures, there is no international consensus on a definition of an 'adequate treatment response' nor on the question 'how to define change?'. Therefore, these issues are addressed in this thesis (chapter 9).

The goal of any intervention to treat drooling is a reduction of visible spill of saliva or a decrease in posterior drooling to improve the child's quality of life and to make caregivers' lives easier. Various non-invasive and invasive treatment strategies for the improvement of oral motor control and reduction of drooling are available. Non-invasive therapies can be categorized into (1) oral (sensory)motor therapies to optimize oral sensation and awareness

of saliva spill, (2) oral-motor strategies to increase swallowing frequency, (3) behavioral (i.e., self-management) techniques, and (4) oral drugs to reduce salivary to increase swallowing frequency and efficacy flow (e.g. anti-cholinergic medication). Invasive interventions comprise (1) intra-glandular injections with botulinum neurotoxin type-A (BoNT-A), and (2) surgical interventions (e.g. duct ligation, gland excision, and redirection of saliva to the posterior part of the mouth).[47] Unfortunately, there is no (international) consensus on the hierarchy of these interventions, when or how to start treatment, or how to continue with treatment in the long run. In collaboration with saliva control teams from the USA, Australia, UK, and the Netherlands, we composed a first, evidence-informed approach to the management of drooling in children and youth with CP (chapter 6).

Previous research

Since 2001, several PhD projects have been completed at the Radboud university medical center addressing different aspects of drooling. Our salivary control and swallowing team was able to proof that BoNT-A in the submandibular glands reduces the salivary flow and anterior drooling in approximately half of the children with neurodevelopmental disabilities for about 22 weeks (median duration).[48-50] In addition, surgery (i.e., submandibular duct relocation, submandibular gland excision and submandibular duct ligation) appeared to be effective and safe to diminish visible drooling.[51-55] We provided evidence that salivary flow reduction has a significant impact on daily life and care, with positive consequences for social interaction and self-esteem.[41, 46, 56] Possible side effects of treatment were also investigated, revealing that after BoNT-A injections for drooling there is a risk of thickened saliva.[57] Non-medical treatment options, e.g. behavioral interventions,[58, 59] were also studied and a self management program for children with appropriate motivation and learning abilities was developed and evaluated.[60, 61] Besides anterior drooling, we were able to show that posterior drooling can just as well be treated by an intervention aimed at saliva reduction.[38, 51] Specific interest in the cause of drooling led to evidence that dysfunctional oral motor control is most likely to be responsible for drooling, because hypersalivation does not occur except in children with a dyskinetic movement disorder.[38] Lastly, our team provided evidence that the outcome of BoNT-A treatment cannot be predicted based on the type of CP, nor on other functional characteristics such as head position, lip seal, tongue control, mental age, or control of voluntary movement.[62, 63]

Outline of this thesis

Although significant progress in the treatment of drooling, eating and drinking problems, and dysphagia has been made, there are still substantial gaps in our knowledge to assess, treat, and monitor children with neurodevelopmental disabilities who suffer from drooling and/or dysphagia. In this thesis we address both the assessment of oral motor performance (part one) and a personalized approach to the treatment of drooling (part two).

Part one: towards refined assessment of oral motor performance:

Chapter 2 describes the development and validation of a parent questionnaire to quantify drooling severity and frequency in young children (the DRIPS). Based on this questionnaire the development of saliva control in typically developing infants and preschoolers is described and sex-specific reference charts are constructed to compare and visualize saliva control with peers. These charts allow clinicians to timely initiate individually targeted interventions if children outperform.

Chapter 3 describes the clinical practice of swallowing problems in cerebral palsy, based on a literature review. A plan for an integrated approach to investigation and treatment of swallowing problems in CP is presented.

Chapter 4 assesses the reliability, validity and usability of a functional classification system for eating and drinking abilities of Dutch children with CP. Use of EDACS by SLTs and parents is investigated and forms the basis for increased awareness of safety and efficiency of eating and drinking abilities in children with CP.

Chapter 5 examines if the 10-minute drooling quotient and the 5-minute drooling quotient are interchangeable. The agreement between measurements of 162 children with neurodevelopmental disabilities and their accuracy in classifying drooling severity were used to develop a time-efficient clinical, objective drooling assessment.

Part two: towards a personalized approach to the treatment of drooling

Chapter 6 reports an evidence-informed approach for the treatment of sialorrhea in children and youth with CP, based on the AACPDM (American Academy of Cerebral Palsy and Developmental Medicine) care pathway.

Chapter 7 presents a case series of children with Megdel syndrome and anterior and posterior drooling. The need for a stepwise and personalized treatment approach is emphasized.

Chapter 8 describes adverse effects of submandibular BoNT-A injections on oral motor function in children with drooling and developmental disabilities due to central neurological disorders. We also tried to identify independent predictors of adverse effects in this population.

In **Chapter 9** we discuss our definition of a clinical response to treatment and critically reflect on what should be considered a meaningful change after BoNT-A treatment. Changes in the impact of drooling on daily life and care, social interaction and self-esteem after BoNT-A treatment are analyzed.

Chapter 10 comprises the summary and general discussion.

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Part one

Towards refined assessment of oral motor performance


2

CHAPTER 2

Development of the Drooling Infants and Preschoolers Scale (DRIPS) and reference charts for monitoring saliva control in children aged 0–4 years

K. van Hulst
L. van den Engel-Hoek
A.C.H. Geurts
P.H. Jongerius
J.J.W. van der Burg
T. Feuth
F.J.A. van den Hoogen
C.E. Erasmus

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Abstract

Objectives: To develop and validate a parent questionnaire to quantify drooling severity and frequency in young children (the Drooling Infants and Preschoolers Scale – the DRIPS). To investigate development of saliva control in typically developing young children in the age of 0–4 years. To construct sex-specific reference charts presenting percentile curves for drooling plotted for age to monitor the development of saliva control in infancy and preschool age.

Study design: The DRIPS was developed consisting of 20 items to identify severity and frequency of drooling during meaningful daily activities. Factor analysis was performed to test construct validity. A piecewise logistic regression was followed by a piecewise linear regression to construct sex-specific reference charts.

Results: We obtained 652 completed questionnaires from parents of typically developing children. The factor analysis revealed four discriminating components: drooling during *Activities, Feeding, Non nutritive sucking, and Sleep.* To illustrate the development of saliva control, eight sexspecific reference curves were constructed to plot the scores of the DRIPS by age group, at the 15th, 50th, 85th and 97th percentile. About 3–15% of the preschoolers in our cohort did not acquire full saliva control at the age of 4 years.

Conclusions: With the DRIPS it is possible to validly compare and visualize the development of saliva control in an individual infant or preschooler and allow clinicians to timely initiate individually targeted interventions if children outperform.

Introduction

Drooling is the unintentional loss of saliva from the mouth and is considered to be a normal phenomenon in the growing child.[1] In general, drooling starts when infants keep up their head in prone position (mean age 2.3 months SD 0.8) or when children start to bring toys to their mouth (mean age 3.3 months SD 1).[2] In typically developing children drooling decreases as a result of maturation of the oral sensory-motor functions.[3] The development of saliva control might be considered as a process of perception-action coupling.[4] Sensory experiences like feeling saliva in the oral cavity or running down the lips or chin, and sensory-based motor actions like learning to slurp a drop from the lips into the mouth and form a saliva bolus before swallowing are considered crucial in the early development of saliva control. Infants and preschoolers have to learn how to couple these perceptual experiences to adequate motor action to change their (drooling) behavior. This process takes place in a responsive environment where social feedback on the negative consequences of drooling is also important to motivate the child to attain saliva control.

Swallowing saliva is a complex function that includes volitional and reflexive actions, needing the integrity of five nerves and 30 muscles.[5] The average saliva flow varies between 0.5–1.5 l per day and flow variation may be dependent on environmental stimuli and conditions like temperature and humidity.[6, 7] It is assumed that salivary flow during infancy is also influenced by teeth eruption, dietary changes, and age (higher flow in older children).[8] In addition, salivary flow is modulated by chewing and increases during the introduction of solid food.[9] As stated before, the growing child will usually adapt to these salivary flow changes by 'implicit motor learning': acquiring skills through practice and refinement. In the end the desired movement (spontaneous saliva swallow) is made automatically during an increasing number of daily activities.[10]

Underlying causes of pathological drooling in young children can be a combination of (1) oral motor difficulties when swallowing, (2) sensory processing problems in the mouth region related to saliva, and (3) insufficient coupling between sensations that arise when the saliva 'spills' and the active swallowing process.[11]

From preschool age on, problems with saliva control may lead to embarrassment in the child and avoidance by peers.[1] Visible drooling is not a medical condition, but it can lead to socio-emotional burden for the child and its parents if it still exists at an older age. The frequently used developmental screening tools and clinical assessment tests in our country (such as the Dutch van Wiechen classification scheme[12] and Bayleys-III-NL[13]) do not document any developmental stages of saliva control in typically developing children. In addition, there is no consensus about the age at which saliva control should be achieved. Some authors argue that it is physiological to drool up to the age of 18 months and that up to the age of 4 years drooling can be tolerated.[1, 14] Others conclude that healthy, typically developing children might have troublesome drooling up to 6 years of age.[15] Yet, Crysdale stated that drooling after the age of 4 years, while

the child is awake, should be considered as abnormal.[16] This is why saliva control teams accept children from the age of 3–4 years for drooling assessment and treatment.[15, 17] It must be concluded that a valid instrument for assessment of the development of saliva control in young children is lacking and that there is no consensus about the age limit at which drooling must be considered problematic. To gain better insight in these issues, the primary objective of this study was to develop and validate a questionnaire for parents to quantify drooling severity and frequency in their young children (the Drooling Infants and Preschoolers Scale – the DRIPS). With the DRIPS, our second goal was to investigate the course of development of saliva control in typically developing children between the age of 0–4 years. The third goal was to construct sex-specific reference charts presenting percentile curves plotted for age to monitor saliva control in infancy and preschool age.

Materials and methods

Development of the DRIPS

Initially, a questionnaire about drooling for parents and other caregivers of young children was developed in Dutch, based on common knowledge about drooling, children's psychomotor development, and the development of saliva control. The first part of the questionnaire consisted of items concerning demographic and health characteristics (items 1–7). Questions about drooling frequency and severity in meaningful situations were included in the second part of the questionnaire (items 8–16). In this part, parents were asked to rate their child's drooling in the following nine context-related situations: in prone position, during supported sitting, during gross motor activities, fine motor activities, eating and drinking, non-nutritive sucking on thumb or pacifier at daytime and night- time, while sleeping, and while babbling or talking. Answers were classified in accordance with the ordinal distribution of the Drooling Frequency and Severity Scale (DFSS).[18] Dichotomous answers about drooling during teething and (nose) colds (items 17–20) were collected in the third part of the questionnaire.

The initial Dutch questionnaire was piloted and its readability for parents was improved on the basis of a study including 119 typically developing children and their parents in 2008, after which consensus for adaptations was reached in the research group. The final Dutch version of the DRIPS was developed in 2009 with the aim to be able to complete the questionnaire in 15 min.

Procedure

Data from postal questionnaires were collected from 2009 to 2012 in convenience sample by sending the questionnaires to day nursery's, child health clinics, playgroups, and parents of young children in the Netherlands. In addition, from 2011 to 2013, data from digital questionnaires were collected via internet home pages and forums for parents with young children in the Netherlands. For the aim of the current paper, an English translation of the

Dutch questionnaire was created using the method of Eremenco et al.[19] (see Appendix A). The following exclusion criteria were applied with regard to sample selection: age > 4;00 years, any diagnosis of oral or facial (anatomical) deficits, any known congenital syndromes or confirmed neurological problems.

Statistics

Descriptive statistics were used to report the demographic data. To evaluate the construct validity of the questionnaire, an exploratory factor analysis was performed to test the underlying dimensions of the DRIPS. Principal component analysis (PCA) was applied as the extraction method. Orthogonal rotation (varimax) with Kaiser's criterion, eigenvalues > 1.0, was used to determine the final number of extracted factors. The Kaiser-Meyer-Olkin (KMO) measure was performed to verify the sampling adequacy for the analysis. In addition, Bartlett's test of sphericity was applied to test if correlations between items were sufficiently large for PCA. A full factor loading matrix for the final solution is presented together with percentages of variance explained by each factor. Cronbach's alpha of items with factor loading ≥ 0.60 were calculated to measure the internal consistency of each factor found. Values of 0.70–0.95 were accepted.[20] To control for the relationship between the four factors, the Pearson product-moment coefficients of correlation between the factor sum-scores were calculated. A moderate to weak relationship ($r < 0.70$) was expected to establish that each factor addressed a separate concept within the total construct.[20] All questionnaire items on drooling were scored on an ordinal scale and finally a sum score for each factor was calculated by adding up the frequency and severity score. A pooled multiple imputation method in SPSS was used to deal with missing values and values coded as "not applicable" (in total < 5% of all answers).

To determine the reference values for girls and boys, two stages were used to construct the sex-specific reference values of each of the sum scores belonging to the factors found in the factor analysis. The large number of zero scores on the factors makes an analysis that assumes normal distributions of scores probably invalid. Therefore, we used two stages to construct the sex-specific reference values for each of the factors.

At first, drooling variables were characterized by an age-specific (large) number of zero values indicating no drooling. Specifically, the theoretical pattern for the first 8 months (0.7 Y) is different from the period thereafter, because then children start crawling, sit without support, while the first teeth occurs, solid food is introduced and children show self-feeding behaviors.[2] Following this reasoning, a piece-wise logistic regression was used, with a change point at the age of 8 months to describe the probability of non-drooling as a function of age. The independent variables were the continuous age variable and a continuous, transformed age variable equal to zero for age < 8 months, and equal to the actual age minus 8 months for the age of 8 months or older.

Second, a piece-wise linear regression was used to study the pattern in non-zero scores of each drooling variable, separately. The dependent variable was the (non-zero) score of the drooling variable of interest. The independent variables were the continuous age variable and a continuous transformed age variable equal to zero for age < 24 months (2.0 Y), and equal to the actual age minus 24 months for age 24 months or older. The change point for the piecewise regression was chosen at 2 years of age, based on the idea that most of the gross, fine and oral motor behaviors should have been developed by that time. Likewise, the eruption of the primary teeth should have been finished.[21]

The age-specific point estimate of the percentage zero of the first stage and the age-specific percentiles in the second stage were combined to calculate the eight-specific reference values. The 15th-, 50th-, 85th- and 97th-percentile are visualized in a graph.

Initially, a wide range of models on drooling variables were studied, namely: first to third degree polynomials in age, piece-wise regression in age, and untransformed and logarithmically transformed values of the drooling variables. The Likelihood-Ratio test was used to test the differences between the models for their goodness of fit to the data.

Statistical analyses were carried out using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA) and SAS 9.2 for Windows (SAS Institute, Cary, NC).

Table 1: Demographic and health characteristics of the study population (*n*=652).

Child characteristics	*n*	(%)
Sex		
Male	314	(48.2)
Female	338	(51.8)
Age groups in months (Male/Female)		
0–3 (23/18)	41	(6.3)
3–6 (21/15)	36	(5.5)
6–9 (23/25)	48	(7.4)
9–12 (28/27)	55	(8.4)
12–15 (21/24)	45	(6.9)
15–18 (22/23)	45	(6.9)
18–21 (17/17)	34	(5.2)
21–24 (13/22)	35	(5.4)
24–27 (24/26)	50	(7.7)
27–30 (15/19)	34	(5.2)
30–33 (24/34)	58	(8.9)
33–36 (16/19)	35	(5.4)
36–39 (16/18)	34	(5.2)
39–42 (23/15)	38	(5.8)
42–45 (12/19)	31	(4.8)
45–48 (16/17)	33	(5.1)
Region of residence in the Netherlands		
North	87	(13.3)
East	232	(35.6)
South	183	(28.1)
West	150	(23.0)
Gestational age at birth		
≤37 weeks	43	(6.6)
>37 weeks	606	(92.9)
Missing	3	(0.5)
Attendance of a physician or allied health professional	171	(26.2)
Pediatric neurologist	7	(1.1)
Pediatrician[a]	102	(15.6)
Ear Nose Throat specialist[a]	51	(7.8)
Speech Language Therapist[a]	27	(4.1)
Physiotherapist[a]	30	(4.6)
No attendance	478	(73.3)
Missing	3	(0.5)
Medication use[b]		
Yes	72	(11.0)
No	580	(89.0)

[a] Attendance of more than one physician or allied health professional is possible.

[b] Medication for allergic reactions, gastric reflux, or respiratory.

Table 2: Summary of exploratory factor analysis of the DRIPS (*n*=652).

Does drooling occur in your child during/in:	Rotated Factor Loadings			
	Activities	***Feeding***	***Non Nutritive Sucking***	***Sleep***
Tummy position	**0.87**	0.09	0.09	0.04
Severity level	**0.89**	0.05	0.09	0.04
Sitting up and supported	**0.86**	0.13	0.18	0.02
Severity level	**0.87**	0.11	0.18	0.02
Moving around	**0.85**	0.17	0.08	0.11
Severity level	**0.86**	0.12	0.08	0.08
Using fine-motor materials	**0.81**		0.14	0.11
Severity level	**0.83**	0.12	0.12	0.09
Babbling/talking	**0.67**	0.39	0.16	0.07
Severity level	**0.69**	0.35	0.14	0.08
Eating and drinking	0.30	**0.89**	0.11	0.11
Severity level	0.33	**0.88**	0.14	0.07
Sucking a pacifier or thumb (daytime)	0.25	0.12	**0.86**	0.03
Severity level	0.24	0.18	**0.86**	0.02
Sucking a pacifier or thumb (nighttime)	0.08	−0.01	**0.65**	0.56
Severity level	0.14	0.01	**0.60**	0.55
Sleeping	0.06	0.05	0.18	**0.90**
Severity level when sleeping on back	0.14	0.00	0.11	**0.73**
Severity level when sleeping on side	0.01	0.10	−0.01	**0.85**
Severity level when sleeping on tummy	0.04	0.07	−0.01	**0.86**
Eigenvalues[a]	**8.68**	**1.35**	**1.63**	**3.48**
% of variance[a]	**43.38**	**6.75**	**8.16**	**17.42**
Cronbach's α[b]	**0.95**	**0.88**	**0.82**	**0.84**

In bold: Rotated factors matrix shows largest loading for each variable per factor.

[a] Values before rotation.

[b] Cronbach's alpha of items with factorloading ≥0.60.

Results

Data collection and participants

In total 676 questionnaires were returned, of which 296 questionnaires were obtained by post (response rate 32.9%) and 380 web-based. Twenty-four questionnaires were excluded based on the pre-set exclusion criteria or because forms were incomplete or filled in with invalid data. Hence, the final study population consisted of 652 typically developing children between 0–4;00 years old (314 boys, 338 girls; see for demographic and health characteristics Table 1). Children were divided in 16 age groups of three months with a minimum of 30 children in each group. There were on average 40.8 children per age group (range 31–58). The total sample was representative for sex, age and region of residence in the Netherlands (see Table 1). To obtain a fair representation of a 'normal' population of typically developing children, we accepted preterm born infants (6.6%), children using medication (11%), and children who attended a physician or allied health professional (26.2%). A small proportion of these children (7%) were treated by more than one physician or allied health professional (7%).

Factor analysis

A principal component analysis (PCA) was conducted on the 20 items with orthogonal rotation (varimax). The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.83, above the recommended value, and Bartlett's test of sphericity was significant (χ^2 (190)= 13521.96, $p < .01$) indicating that correlations between items were sufficiently large for PCA.

An initial analysis was run to obtain eigenvalues for each component in the data. Four components had eigenvalues over Kaiser's criterion of 1 and in combination explained 75.7% of the variance. Table 2 shows the factor loadings after rotation. The items that cluster on the same components suggest that factor 1 represents drooling during *Activities* (prone position, sitting with assistance, gross motor activities, fine motor activities, and babbling/ talking (items 8–11 and item 16)), factor 2 represents drooling during *Feeding* (item 12), factor 3 drooling during *Non nutritive sucking* during day and night (items 13–14), and factor 4 drooling while *Sleeping* in different positions (item 15). All factors showed high reliability (all Cronbach's α–values > 0.82) and the Pearson's correlation coefficients between the factors were significant, though moderate to weak (factor 1–2: r_p=0.52, factor 1–3: r_p=0.40, factor 1–4: r_p=0.15, factor 2–3: r_p=.35, factor 2–4: r_p=0.15, factor 3–4: r_p=0.39)

Sex-specific reference charts

As a result of the combined regression analysis, percentile curves for all factors were calculated for each sex-specific age group and presented in Fig. 1. The curves for the factors *Activities, Feeding* and *Non nutritive sucking* showed a descending trend; older children drool less than younger children. Curves for the factor *Sleep* showed a rising trend.

Drooling during activities

At the age of 35 months, 50% of the boys achieved a sum score of 0 (no drooling) during *Activities*, whereas girls reached that score already at the age of 30 months. Fifteen percent of the boys still had some drooling (DRIP score ≥ 5) at the age of 4 years, whereas this score was ≥ 2 for the girls. At the age of 4 years drooling still occurred in 3% of the boys and girls with respective sum scores of ≥ 15 and ≥ 11.

Drooling during feeding

In 50% of the cases (boys and girls) drooling during *Feeding* stopped at the age of 21–22 months and only 3% of the preschoolers drooled during mealtimes with a score of 3–4 at the age of 4 years. In 85% of the girls, drooling during feeding ended before the age of 4 years, whereas 15% of the boys still drooled with a score ≥ 2 at the age of 4 years.

Drooling during non nutritive sucking

Drooling during *Non nutritive sucking* on thumb or pacifier stopped in 50% of the boys at 36 months and in 50% of the girls at 29 months. Both boys and girls still drooled in 15% of the cases during *Non nutritive sucking* with a score ≥ 3–5 at the age of 4 years and 3% persisted drooling during *Non nutritive sucking* at that age (score ≥ 6–7).

Drooling during sleep

The curves of drooling during *Sleep* have an ascending line. Still 50% of the children drooled at the age of 4 years with scores ≥ 5 for boys and ≥ 3 for girls.

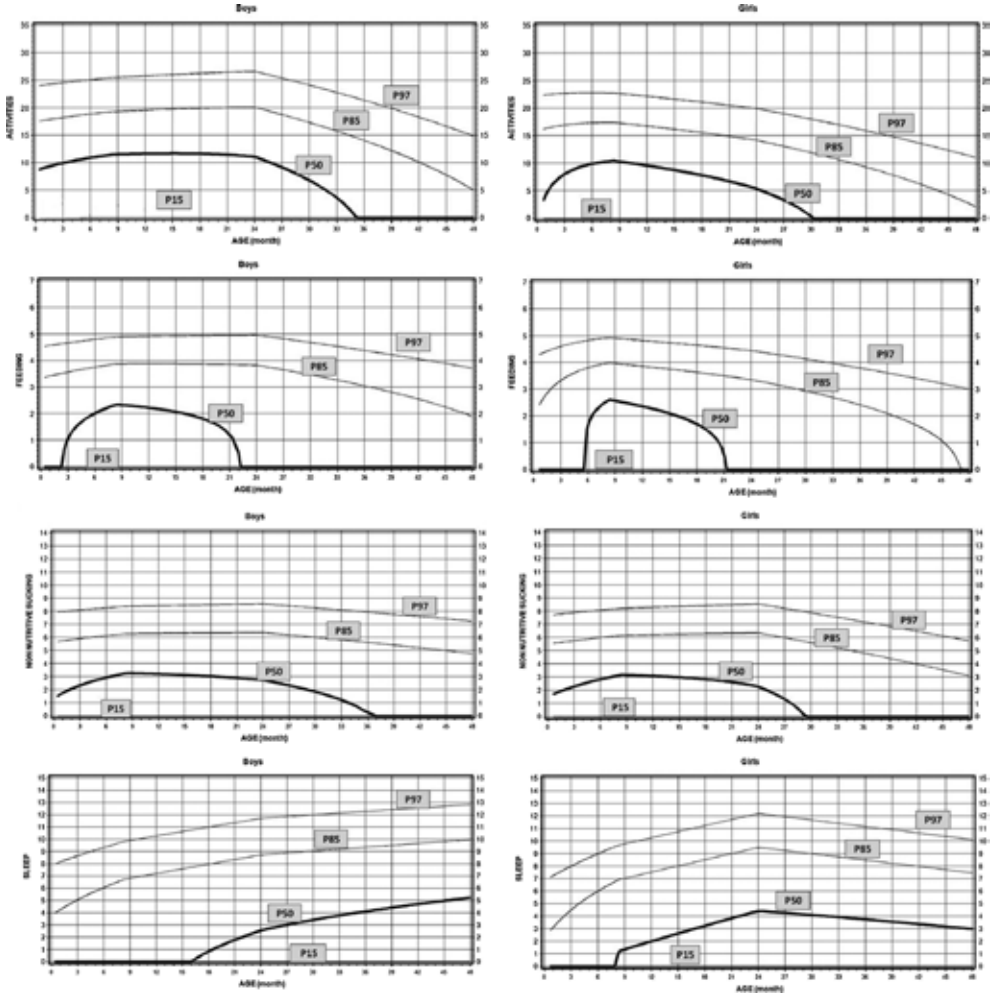

Figure 1. Sex-specific reference charts with percentile curves (P15th, P50th, P85th, P97th) for the factors drooling during *Activities, Feeding, Non nutritive sucking* and *Sleep*.

Discussion

To the best of our knowledge this is the first study that analyzed drooling and the development of saliva control in a large representative cohort of typically developing infants and preschoolers up to 4;00 years. Data were collected with a newly developed parent questionnaire, the Drooling Infants and Preschoolers Scale – DRIPS. In addition, sex-specific percentile curves for drooling in four situations were developed for children in different age groups. These can be easily used in clinical practice to compare children of the same sex and age with their peers regarding the severity and frequency of problems with saliva control.

Although Crysdale[16] stated that drooling must be considered abnormal after the age of 4 years, we found that a substantial part (3–15%) of the typically developing preschoolers are still drooling to a certain extent at 4 years of age. We speculate that not all these children suffer from abnormal pathological drooling, but that drooling in a small group of children older than 4 years is within the range of normal variability. Special attention and monitoring should be given to the 3% children with a percentile > P97 who could be at risk of pathological drooling.

Differences were found between boys and girls in the course of the development of saliva control. For example, half of the female population stopped drooling earlier than their male peers during *Activities*. Miller et al.[22] already found significant prenatal sex differences for laryngeal and pharyngeal motor activity and oral-lingual movements, suggesting a sex-dependent trajectory of oral motor development. Other studies have also suggested that there are maturational sex differences in motor skills of preschoolers and that preschool boys and girls should not be compared to each other, but to children of the same age and sex.[23, 24] Because we anticipated that sex differences in motor skill development between preschool boys and girls might also influence children's drooling behavior, we presented sex-specific references charts. At the age of 4 years, however, sex differences in drooling behavior tends to taper off, as is demonstrated in these curves.

Saliva control was first achieved during *Feeding*, even though it is known that salivary flow rates increase during eating. During normal development, children from 12 to 36 months of age refine their oral motor skills during feeding and become more effcient in moving the jaw, lips and tongue to gain oral motor control and to form a bolus.[25] The oral phase of swallowing during feeding or saliva swallowing takes place in two stages: a suction or collecting stage and a propulsion stage.[26] Lespargot et al. found that the oral suction stage of saliva swallowing in healthy children is characterized by intra-oral pressure.[26] This intra-oral pressure is generated by combined movements of the tongue and mandible and is necessary to collect saliva or small volumes of liquid and to form a bolus. These findings were confirmed by a study of Bourdiol et al. who identified three different saliva swallowing patterns.[27] In all patterns, intra-oral negative pressure played an important role in gathering saliva above the tongue and in the propulsion of the saliva bolus into the pharynx. The same mechanism of suction, food bolus formation and propulsion to clean the oral cavity is seen during eating and drinking. Probably, because swallowing saliva and swallowing food tend

to develop synchronously, saliva control during *Feeding* is the first factor achieved in 50% of the children aged 21–23 months.

Our data show that drooling still exists in 15% of 4-year-old boys and girls during *Non nutritive sucking* on their thumb or pacifier. The percentile curves P85th and P97th stay rather flat, which implies that these children do not achieve full saliva control when they continue thumb or pacifier sucking. To our knowledge, limited data are available concerning the relation between thumb or pacifier sucking and drooling in typically developing infants and preschoolers. In a study of Szynkiewicz et al., the rate of non nutritive swallowing during awake state in infants while sucking 10 min on their pacifier was compared with the swallow rate without pacifier.[28] In both the younger group (age 2–4 mo) and the older infants (age 7–9 mo), the use of the pacifier doubled the rate of swallows. This is in accordance with our data. The curves for *Non nutritive sucking* show an upward trend during the first nine months, which implies that children suck and swallow saliva frequently during thumb or pacifier sucking. After that period, non nutritive sucking seems to maintain drooling behavior in young children. This is probably because they habituate to the pacifier or thumb without a trigger to collect and swallow saliva. During non nutritive sucking the lips are slightly opened, the tongue is in a low position, and swallow efficiency (in terms of making intra-oral pressure and collecting saliva) is limited. As a consequence, children do not practice saliva control during non nutritive sucking. As repetitions are essential for the acquisition of (oral) motor skills[10], this is an important reason for health professionals to advice parents of children who still drool to stop their child's habit of thumb or pacifier sucking.

Although salivary flow is low during sleep,[7] all drooling curves (of boys and girls) during *Sleep* in different positions rise during the first 4 years. From this, we conclude that drooling during *Sleep* may not subside with age and may not be related to the development of saliva control. This makes the factor *Sleep* different from the others that all are clearly related to development.

A strength of this study is the use of factor analysis to test construct validity of a parent questionnaire, allowing the identification of constructs underlying saliva control development. The sample size of this cross-sectional study is large and the participants are reasonably representative of the Dutch population of 0–4 years of age. Indeed, the percentage of preterm born children in this study (6.6%) is close to the percentage of preterm born infants in the Dutch population (7.4%).[29]

A limitation of this study is the fact that the assessment of drooling behavior is only based on parent questionnaires. However, it has been proven that parent-report observations can be used to monitor the child's (gross) motor development.[30] In addition, our participant inclusion may have been biased if parents of children with troublesome drooling felt more need to fill in and return the questionnaire than parents of children without troublesome saliva loss.

Conclusion

The acquisition of saliva control should be considered as an integral part of normal development during childhood. It is associated with physical growth and maturation of the oral sensory and motor functions, by motor learning based on perception-action coupling, and by increasing cognitive and social-emotional awareness. Knowledge about the development of saliva control and the availability of reference charts for drooling severity in infants and preschoolers is important for pediatric physicians, therapists, and multidisciplinary saliva control teams. The DRIPS enables communication with parents about the impact of their child's drooling and the development of saliva control compared to peers. In the event of delayed saliva control a proper treatment can be started. The sexspecific reference charts of the DRIPS from our study allow health professionals to monitor the developmental stages of drooling behavior up to the age of 4 years and timely initiate individually targeted interventions. Percentile curves derived from DRIPS scores of children developing typically may be useful for screening. We suggest to use the 97th percentile as the outer most percentile cutoff value indicating pathological drooling. Children with DRIPS scores above the 85th percentile could be considered as 'at risk'.

If a child drools significantly more than his peers, individual advice can be given to train specific skills. For example, high scores on drooling during *Activities* are possibly related to immature motor skills and referral to a pediatric physiotherapist may be beneficial. If a child shows excessive drooling during *Feeding*, there may be underlying oral-motor problems for which it is wise to consult a speech-language therapist. When a child scores high on all factors, a general health issue (e.g. ear-nose-throat pathology) or an overall developmental delay may be an underlying cause. However, whether the DRIPS is a useful instrument to improve clinical practice, needs to be proven in further longitudinal studies, testing the stability of the percentile curves including both typically developing children and children with excessive pathological drooling behavior.

Acknowledgement

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Appendix A. DRIPS questionnaire

zie voor bestand:
www.radboudumc.nl/drips

Drooling Infant and Preschooler Scale (DRIPS)

Parent section

Radboudumc

To the parents/guardians,
You are asked to complete this survey because drooling occurs in your child. The purpose of this questionnaire is to find out what elements may be a factor to drooling. Kindly fill out this questionnaire based on the past two weeks.
Each question is made up of two parts. The first part contains a question about *when* drooling occurs in your child, the second part covers the *level of drooling*. If, for example, your child never plays in a tummy position (question 8), you may tick N/A (not applicable).

Part 1.

1. Your child's name: _____

2. Date of completion:____-____-_____

3. What is your child's date of birth?
____-____-_____

4. What is your child's gender?
□ Boy
□ Girl

5. Was your child born before week 37 of your pregnancy?
□ Yes
□ No

6. Has your child visited: *(several answers possible)*
□ The (pediatric) neurologist concerning:_____.
□ The pediatrician concerning:_____.
□ The Ear Nose Throat specialist concerning:_____.
□ The speech therapist concerning:_____.
□ The physiotherapist concerning:_____.
□ None of the above

7. Does your child take any medication?
□ Yes, i.e.:_____.
□ No

Part 2.

8. Does drooling occur in your child while in a tummy position and awake, e.g. when playing on the floor?
□ Never □ Occasionally □ Often □Always □ N/A
(Proceed to question 9) *(Proceed to question 9)*

What is the level of drooling?
□ Wet lips □ Wet lips and chin □ Also wet clothes/bib □ Wet clothes, hands, table, floor and items

9. Does drooling occur in your child while sitting up and supported (supported by the parent or sitting in a chair with a back)?
□ Never □ Occasionally □ Often □Always □ N/A
(Proceed to question 10) *(Proceed to question 10)*

What is the level of drooling?
□ Wet lips □ Wet lips and chin □ Also wet clothes/bib □ Wet clothes, hands, table, floor and items

10. Does drooling occur in your child while moving around, e.g. rolling over, crawling, walking, jumping or doing sports?
□ Never □ Occasionally □ Often □Always □ N/A
(Proceed to question 11) *(Proceed to question 11)*

What is the level of drooling?
□ Wet lips □ Wet lips and chin □ Also wet clothes/bib □ Wet clothes, hands, table, floor and items

11. Does drooling occur in your child while using fine-motor materials such as a rattle, blocks, while drawing, stringing beads?
□ Never □ Occasionally □ Often □Always □ N/A
(Proceed to question 12) *(Proceed to question 12)*

What is the level of drooling?
□ Wet lips □ Wet lips and chin □ Also wet clothes/bib □ Wet clothes, hands, table, floor and items

12. Does drooling occur in your child while eating and drinking?
□ Never □ Occasionally □ Often □Always
(Proceed to question 13)

What is the level of drooling?
□ Wet lips □ Wet lips and chin □ Also wet clothes/bib □ Wet clothes, hands, table, floor and items

13. Does drooling occur in your child while sucking on a teat, thumb, finger, lip or pacifier during the day?
□ Never □ Occasionally □ Often □Always □ N/A
(Proceed to question 14) *(Proceed to question 14)*

What is the level of drooling?
□ Wet lips □ Wet lips and chin □ Also wet clothes/bib □ Wet clothes, hands, table, floor and items

14. Does drooling occur in your child while sucking on a teat, thumb, finger, lip or dummy during the night?
□ Never □ Occasionally □ Often □ Always □ N/A
(Proceed to question 15) *(Proceed to question 15)*

What is the level of drooling?
□ Wet lips □ Wet lips and chin/cheeks □ Also wet clothes □ Also wet pillows, sheets and cuddly toys

15. Does drooling occur in your child while it is asleep?
□ Never □ Occasionally □ Often □ Always
(Proceed to question 16)

What is the level of drooling when your child sleeps on its back? □ N/A
What is the level of drooling when that's the case?
□ Wet lips □ Wet lips and chin/cheeks □ Also wet clothes □ Also wet pillows, sheets and cuddly toys

What is the level of drooling when your child sleeps on its side? □ N/A
What is the level of drooling when that's the case?
□ Wet lips □ Wet lips and chin/cheeks □ Also wet clothes □ Also wet pillows, sheets and cuddly toys

What is the level of drooling when your child sleeps on its tummy? □ N/A
What is the level of drooling when that's the case?
□ Wet lips □ Wet lips and chin/cheeks □ Also wet clothes □ Also wet pillows, sheets and cuddly toys

16. Does drooling occur in your child when babbling/talking?
□ Never □ Occasionally □ Often □Always □ N/A
(Proceed to question 17) *(Proceed to question 17)*

What is the level of drooling when that's the case?
□ Wet lips □ Wet lips and chin □ Also wet clothes/bib □ Wet clothes, hands, table, floor and items

Part 3.

17. Has your child had (new) teeth eruptions over the past two weeks?

□ Yes
□ No *(Proceed to question 19)*

18. Would you have completed the survey differently if your child had not had (new) teeth eruptions over the past two weeks?

□ Yes, my child tends to suffer more from drooling.
□ Yes, my child tends to suffer less from drooling.
□ No

19. Has your child had a cold (in the nose) over the past two weeks?

□ Yes
□ No *(End of survey)*

20. Would you have completed the survey differently if your child had not had a cold (in the nose) over the past two weeks?

□ Yes, my child tends to suffer more from drooling.
□ Yes, my child tends to suffer less from drooling.
□ No

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3

CHAPTER 3

Clinical practice

Swallowing problems in cerebral palsy

C.E. Erasmus
K. van Hulst
J.J. Rotteveel
M.A.A.P. Willemsen
P.H. Jongerius

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Abstract

Cerebral palsy (CP) is the most common physical disability in early childhood. The worldwide prevalence of CP is approximately 2–2.5 per 1,000 live births. It has been clinically defined as a group of motor, cognitive, and perceptive impairments secondary to a non-progressive defect or lesion of the developing brain. Children with CP can have swallowing problems with severe drooling as one of the consequences. Malnutrition and recurrent aspiration pneumonia can increase the risk of morbidity and mortality. Early attention should be given to dysphagia and excessive drooling and their substantial contribution to the burden of a child with CP and his/her family. This review displays the important functional and anatomical issues related to swallowing problems in children with CP based on relevant literature and expert opinion. Furthermore, based on our experience, we describe a plan for approach of investigation and treatment of swallowing problems in cerebral palsy.

Introduction

Cerebral palsy (CP) is the most common physical disability in early childhood. The worldwide prevalence of CP is approximately 2–2.5 per 1,000 live births.[27] It has been clinically defined as a group of motor, cognitive, and perceptive impairments secondary to a non-progressive defect or lesion of the developing brain.[4] Epilepsy is a common problem in patients with CP.[27] Up to 80% of CP cases arise from antenatal factors; birth asphyxia contributes approximately 10% of CP cases.[16] Acquired cases in the postnatal period are usually related to central nervous system infection, trauma, strokes, and severe hypoxic events such as neardrowning. Genetic disorders and acquired insults follow a pattern of selective vulnerability during early brain development. For example, the neonatal neuropathological correlates of hypoxic–ischemic encephalopathy include specific and well-known patterns of brain injury[12, 51] (see Table 1) that interfere with the frontal/insular–basal ganglia–brainstem swallowing pathway.[6, 10, 13, 15, 19–21, 23, 24, 26, 39, 52] We propose that an understanding of paediatric dysphagia might be facilitated by a heightened awareness of the topography pertaining to the neuronal damage. This article focuses on the pathophysiology, clinical features, assessment, and management of swallowing problems in children with CP.

Members of the Multidisciplinary Outpatient Swallowing/ Drooling Clinic at the Radboud University Nijmegen Medical Center in the Netherlands continually review literature on dysphagia and drooling in neurologically affected patients. References for this review were obtained from personal reprint files, supplemented by PubMed and Scopus searches with varying search periods. The search terms “drooling,” “sialorrhoea,” “swallowing,” “dysphagia,” “cerebral palsy,” “children,” “brain regions,” “fMRI,” “MEG,” and “EMG” were used. Only English-language articles, published from 1970 up to 2011, were included. The final reference list was generated based on originality and relevance to the topics covered in the review.

Table 1: Regions with a predilection for hypoxic–ischemic neuronal injury to swallowing.

Site of lesion [12, 51]	Swallowing elements[a]		
	Oral	Pharyngeal	GOR
Periventricular leucomalacia (preterm babies)	+	+/−	+/−
Cortical and subcortical injury in a watershed parasagittal distribution (term babies and prolonged partial hypoxic events)	+	+/−	+/−
Relatively selective injury to the putamen, thalamus, and peri-rolandic cerebral cortex, and often including injury to the brainstem (term babies and acute anoxic events)	+	++	+/−

GOR gastro-oesophageal reflux, +/− probably present, + very likely present, ++ evident
[a] Expert opinion

Neural control of swallowing

Normal swallowing is a goal-directed sequential behaviour that requires the coordinated action and inhibition of the muscles located around the oropharynx and oesophagus. The swallowing process is controlled in a complex manner involving the brainstem as well as cortical and subcortical central pathways. In addition, it requires a higher level of fine-tuning between the central circuits and the enteric nervous systems (ENS) (see Fig. 1).

Efficient swallowing relies on sensory input from the oropharynx that triggers bilateral afferents in specific regions of the trigeminal sensory nuclei. Subsequently, the inputs reach the brainstem regions responsible for the patterned motor actions of swallowing. Sequential and rhythmic patterns of swallowing are formed and organized by a central pattern generator (CPG) located in the medulla oblongata. The CPG consists of two hemi-CPGs which, under physiological conditions, are tightly synchronized. The swallowing motor sequence is primarily generated in the ipsilateral hemi-CPG which transfers premotor neuron signals to the contralateral CPG.[17] The CPG itself is organized into two groups of neurons: the dorsal swallowing group (DSG) in and around the nucleus of tractus solitarius (NTS) and the ventral swallowing group (VSG) just cranial to the nucleus ambiguus. The DSG contains the generator neurons involved in the triggering, shaping, and timing of the sequential or rhythmic swallowing pattern. The DSG activates all VSG premotor neurons, which in turn distribute the swallowing drive to the various motor neuron pools involved in swallowing. The multifunctional pattern-generating circuits of the brainstem allow rapid modulation of orofacial behaviours (swallowing, respiration, chewing, coughing, and vomiting).[5]

Although our knowledge of the cortical regions involved in swallowing has grown substantially through functional magnetic resonance imaging studies, the exact central control mechanism for swallowing is still not fully understood. The involvement of many functionally and spatially different cortical sites suggests multilevel control for the swallowing pathways. It has been proposed that the control system consists of parallel loops which are able to coordinate and integrate the complex, sequentially based activation for swallowing.[26] The primary motor area and cingulate and insular cortices might all have essential roles in the coordination of the entire swallowing process.[21, 24, 52] Some investigators assume a functional dominance in swallowing[8] or a time-dependent shift of cortical activation from the left to the right sensorimotor cortex during voluntary swallowing.[45]

In summary, voluntary and reflexive swallowing are controlled by widely distributed bilateral and multifocal cortical networks which apparently involve overlapping cortical regions. The primary sensory, motor, and cingulate cortices have a major role in these networks. The execution of the sensorimotor aspects related to swallowing relies on functionally connected pathways between (extra) pyramidal cortical motor planning

regions, centers controlling the brainstem and cranial nerves, as well as lower motor neurons.

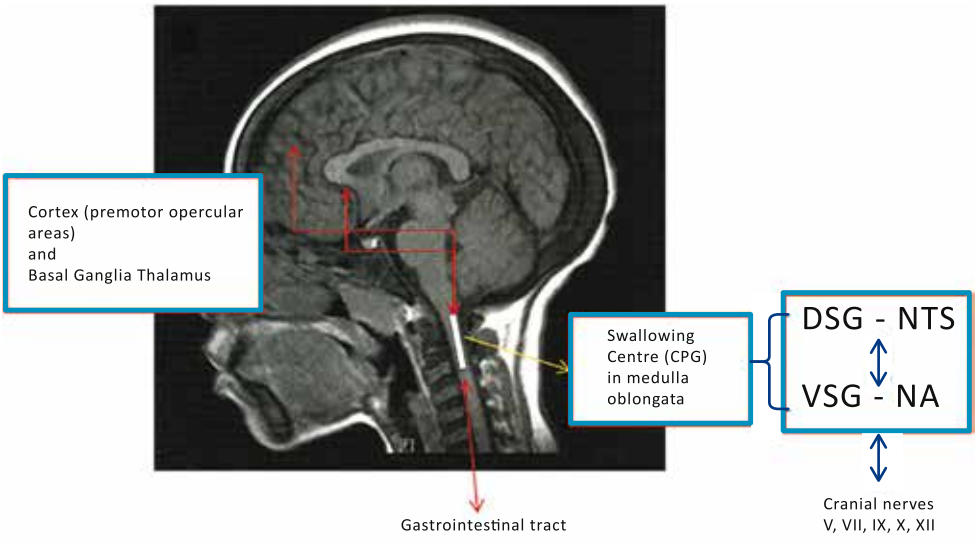

Figure 1. Overview of the swallowing pathway. DSG dorsal swallowing group, NTS nucleus of tractus solitarius, VSG ventral swallowing group, NA nucleus ambiguus.

The brain–gut axis

Normal gastrointestinal tract (GI) function results from a balanced interaction between the enteric nervous system (ENS) and the central nervous system (CNS) which is called "the brain–gut axis". Both neural and hormonal ENS communications have important integrative functions. A detailed discussion of the hormonal pathways is beyond the scope of this article. The ENS neural communications consist of the intrinsic afferent and motor neurons distributed along the gut wall (located in the mesenteric Auerbach and submucosal Meissner plexuses).

Afferent (vagal) sensory fibres terminate in the NTS of the hindbrain. The preganglionic motor innervations to the plexus arise from the dorsal motor nucleus of the vagus in the brainstem. The NTS and the vagal dorsal motor nucleus together comprise the dorsal vagal complex, important in the coordination of the muscular gut activity (by the vago-vagal reflex).[1]

The oesophagus consists of a proximal striated muscle portion (upper oesophageal sphincter, UOS) and a distal smooth muscle portion (lower oesophageal sphincter, LOS). At rest both sphincters are tonically contracted. Relaxation of the UOS (glossopharyngeal and vagal nerves) is initiated in the swallowing center located in the medulla. Relaxation and contraction of the LOS (vagal and splanchic nerves) are initiated through local peristaltic activity of the oesophagus or distension of the gastric wall.

Thus far, the exact coupling of distinct interneurons (also called local circuit neurons or connector neurons) in the NTS is not known. Also, it is not totally clear which cortical regions are mainly involved in processing information to the GI tract. It has been suggested that the anterior insular cortex (called "visceral cortex"), the prefrontal and sensory/motor regions, the cingulate gyrus, as well as the limbic regions, all participate in the integration of neuronal information to the GI tract.[18]

Swallowing problems in cerebral palsy

A recent epidemiological study among 1,357 children recorded by the Northern Ireland Cerebral Palsy Register between 1992 and 2009 showed a dysphagia prevalence of 43% in children with CP in any degree.[29] Results from speech pathology testing and video fluoroscopic swallowing studies in CP children demonstrate the relationship between typically affected brain regions and the associated characteristic patterns of dysfunctional swallowing (see Table 1). Usually, clinical features such as delayed initiation and segmented swallowing during attempted volitional movement might be determined by cortical neuronal networks, while dysfunctional pharyngeal components of swallowing (i.e. automatic components of deglutition, such as throat clearing, laryngeal closure tasks) suggest subcortical brain injury and/or basal ganglia necrosis.[23] In CP, dysphagia is often characterized by problems in both the volitional oral movements and the more reflexive pharyngeal phase of swallowing. Moreover, impaired ability to plan and coordinate swallowing with ventilation (e.g. greater propensity to swallow at abnormal times within the respiratory cycle, such as early inspiration after a thin liquid swallow and variable duration of the deglutition apnoea) are consistent with brainstem involvement.[6] A clinico-pathological correlation between differences in the breath–swallow pattern and the risk for aspiration is likely. Clinically, aspiration or episodic aspiration manifests as frequent coughing and occasional pneumonia. The overall incidence of pulmonary aspiration in CP due to oral motor dysfunctions is not known precisely. Admission to the hospital for presumed aspiration pneumonia in children with CP is common. An earlier study among 238 children with recurrent pneumonia showed that 48% had oropharyngeal incoordination with an aspiration syndrome whereas 50% of these children were diagnosed with CP.[28] Video fluoroscopic study of swallowing (VFSS) has demonstrated pulmonary aspiration in 38%[32] to over 70% of the cases[25], and frequently, the aspiration occurred without coughing, referred to as "silent".[32, 38] Repeated pulmonary aspiration leads to chronic coughing, sleep-disordered breathing, impaired clearance of airway secretions, colonization of the respiratory tract by pathogenic bacteria, and a high risk of progressive lung parenchymal damage. This process may be lethal.[14, 22]

Besides dysphagia, chronic pulmonary aspiration may also occur as a result of the gastro-oesophageal reflux (GOR).[53] The incidence of GOR has been estimated at approximately 50%[40] and might be explained by lesions in the neuronal-anatomic swallowing center located in the medulla oblongata leading to dysfunction of the vago-vagal reflex. In

Table 2: Recommendations for evaluation of dysfunctional swallowing (expert opinion)

The paediatric neurologist, paediatrician, rehabilitation specialist, speech pathologist, ENT specialist, pedagogue, dentist, nurse practitioner, occupational therapist, physiotherapist, plastic surgeon may be involved in the multidisciplinary swallowing/drooling teams.
Assessments:
Medical and social–emotional history of the patient. Does the child suffer from intractable seizures?
Medication, benzodiazepines or neuroleptic-induced drooling?
Respiratory status (cough, wheezing, recurrent pneumonia) → Consider examination by the paediatric pulmonologist.
Comment: although common practice, the prophylactic use of antibiotics with suspected or proven aspiration is not recommended.
Presence of gastro-oesophageal reflux, which, if severe, can be associated with hyperstimulation of the salivary glands or indirect aspiration → Consider GOR treatment.
Nutrition and hydration. Safe feeding programme? Does the feeding result in normal growth? → Consider nasotube feeding, laxative.
Comment: see www.LifeExpectancy.org/articles/GrowthCharts.shtml and [9]
Neurological examination (consciousness, cranial nerves, general motor skills/posture, and tone)
Orofacial examination (nasal breathing, upper airways obstruction) → Consider examination by the ENT specialist.
Oral hygiene, occlusion, and dental examination
Assessment by a speech pathologist → objective: modify food bolus such as consistency, size and texture, positioning of the patient, and examining compensatory swallow manoeuvres:
Posture and head control; mouth closure, lip seal
Oral sensorimotor examination (tongue lateralisation, sensation, tone, strength, (pathological) reactions)
Oropharyngeal stage of swallowing during eating and drinking (swallow on demand, oral control, frequency/efficiency/safety)
Speech (dysarthria/dyspraxia) and communication skills
Management of secretions → Consider drooling treatment [31].
VFSS confirms silent aspiration and defines the pathophysiology of oropharyngeal swallow with various types of bolus
Comments: VFSS is the study of choice for complete evaluation of the feeding and swallowing process; aspiration is suspected in case of recurrent pneumonia and in children who are prone to gagging and coughing; silent aspirators do not exhibit overt symptoms of aspiration; aspiration risk is increased in non-ambulant children with CP (Gross Motor Functioning Classification System III or higher). See also [2]

Table 3: Drooling treatment (expert opinion)

Severe anterior drooling • <3 years: oral motor therapy for training motor skills • >4 years: botulinum toxin therapy (submandibular glands) [36]
If no response or developmental progress → Consider 1. Injection of the submandibular and parotid glands concurrently 2. Intense behavioural treatment [47] 3. Surgery: submandibular duct relocation [37]
Comment: Behavioural therapy is not given nor indicated in adults because no research is done in this field: no evidence exists that it is effective.
Posterior drooling • <3 years: oral motor therapy, feeding advices for safer swallowing • >4 years: botulinum toxin therapy (submandibular and/or parotid glands)
If no response → Consider surgery (duct ligation or gland removal, no submandibular duct relocation)
Comment: Consider anticholinergic medication for drooling control in case of contraindications to botulinum toxin therapy or surgery. Glycopyrrolate (glycopyrronium bromide) appears to be a more acceptable anticholinergic drug in the management of drooling in children. Randomized controlled trials with this drug in children with CP are warranted. Dosage: oral suspension 40–100 µg/kg per day with a maximum of 175 µg/kg per day, dosage given once daily [42]

addition, GOR in children with CP may also result from direct lesions in cortical areas that modulate brainstem activity.[1, 3]

Constipation, a common dysmotility disorder of the gut in children with CP, is often overlooked. More than half of the children with severe generalized CP are constipated.[50] The high incidence of the dysmotility disorders emphasizes the defective integration and modulation of information in the brain–gut axis in CP,[30, 34, 35, 41, 43, 49] for which some investigators had proposed the term "Dysphagia–GOR complex" with a central role for the vagal nerve.[33, 34] It is reasonable to assume that vagal disruption is responsible for defective feedback to the distinct cortical regions and to the brainstem, those features being associated with swallowing disorders, defective ventilation, as well as dysmotility problems. At this time, more studies are needed to investigate the clinical relevance of integrated breathing, GI and swallowing function on the health and nutritional outcomes of children with CP.

Drooling is caused by the swallowing disorder and occurs in 10–58% of children with CP.[11, 44, 46] From a clinical point of view, it makes sense to distinguish between "anterior" and "posterior" drooling. Anterior drooling is the unintentional loss of saliva from the mouth; it can impose a significant disability on children with CP, leading to psycho-social, physical, and educational consequences. The most severely affected children may be rejected by their peers and even by their caregivers. Excessive anterior drooling damages books, computer, and keyboards and as such threatens essential tools for education and communication in neurologically disabled patients. In addition to cosmetic effects, drooling can produce peri-oral infections and can impair dentition. In contrast to anterior drooling, the so-called "posterior drooling" refers to the spill of saliva over the tongue through the faucial isthmus.[18] In particular, the children with most severe pharyngeal dysphagia are at medical risk due to saliva aspiration to the lungs. As mentioned above, aspiration in a child with CP often occurs without obvious coughing or choking (i.e. silent), and therefore, chronic aspiration of saliva might not be diagnosed prior to development of significant lung injury.

In case of chemical irritation such as that caused by GOR, salivary secretion is increased to protect the oral, pharyngeal, and oesophageal mucosa mediated by the vago-vagal complex in the brainstem. Unfortunately, in children with oral motor dysfunction, this protective increased saliva volume may accumulate in the pharynx and/or oesophagus, leading to an increased risk for aspiration. It is still a matter of debate whether GOR can cause severe drooling and whether or not treatment of pathological GOR diminishes drooling in children with CP.

Assessment and management of swallowing problems in CP

The investigation and treatment of swallowing problems in children with CP are challenging. Individualized care plans should be formulated accounting for the degree of oral motor impairment, feeding ability, aspiration, epilepsy, and ambulation. Generally, swallowing is more problematic in non-ambulatory children with CP. Furthermore, marked disturbed consciousness such as drug overdose and seizures interfere with the voluntary swallowing

act and is a common cause of aspiration. Some children develop aspiration in association with GOR. Some anti-epileptics, such as clobazam and clonazepam, and neuroleptic drugs will induce the drooling risk.

In short, there is a growing awareness among clinicians that at early stage, particular note should be given to the importance of dysphagia[7] and excessive drooling contributing substantially to the burden of a child with CP and his or her family.[48] Ideally, the management of patients with swallowing problems requires the coordinated expertise of a number of health care professionals. Regular reassessment is necessary to gauge the response to oral motor training, nutrition, and drooling interventions. Tables 2 and 3 summarize our recommendations for evaluation and treatment of dysfunctional swallowing and drooling in children with CP.

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4

CHAPTER 4

Reliability, construct validity and usability of the Eating and Drinking Ability Classification System (EDACS) among Dutch children with Cerebral Palsy

K. van Hulst
D.A.C. Snik
P.H. Jongerius
D. Sellers
C.E. Erasmus
A.C.H. Geurts

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Abstract

Purpose: To assess the interrater reliability, construct validity and usability of the Eating and Drinking Ability Classification System (EDACS) among Dutch children with Cerebral Palsy (CP) when used by speech and language therapists (SLTs) familiar and unfamiliar with the child's eating and drinking performance and parents.

Methods: Translation was undertaken using the method of Eremenco. Agreement between SLTs and parents when using EDACS was determined by intraclass correlation coefficient (ICC) and linear weighted Kappa (W). Associations with other functional classification systems including the Dysphagia Management Staging Scale (DMSS) were investigated to determine construct validity by Kendall's tau-b.

Results: Thirty-one SLTs classified 149 children (67 girls; mean 10 y, SD 4 y, range 3–21 y) with EDACS. Pairs of SLTs showed good agreement ([ICC] = 0.84; 95% confidence interval [CI] 0.79–0.88; [W] = 0.71). Eighty-one parents showed good agreement with SLTs (n = 31) as well (ICC = 0.80; 95% CI 0.71–0.87; W = 0.61). There was a significant and strong positive correlation of EDACS with DMSS (Kendall's tau-b 0.81) supporting its construct validity. Usability of EDACS was generally good.

Conclusion: The Dutch version of EDACS is reliable and valid, and can be used easily by (familiar and unfamiliar) SLTs and parents of children with CP. Parents and professionals showed a high level of consistency when classifying eating and drinking abilities. EDACS enables uniform and efficient communication about safety and efficiency of functional eating and drinking ability in clinical and research contexts.

Introduction

Cerebral palsy (CP) is a common neurological development disorder with a worldwide prevalence of approximately 2–2.5 per 1,000 live births.[1] People with CP suffer from a range of activity limitations arising from disorders of movement and accompanying disturbances of sensation, perception, cognition, communication and behaviour. Impairments of movement, sensation and posture can limit oral skills required for speech, eating, drinking and swallowing. Bulbar and oral movement difficulties, that may lead to problems with eating and drinking, are common in individuals with CP.[2] International prevalence estimates range from 27–99%, depending on the study population and measures of eating and drinking ability adopted.[3-5]

It is often assumed that there is a significant correlation of oral motor dysfunction affecting speech, eating, drinking and swallowing with the severity of limitations to gross motor function and mobility.[2,3,6-8] According to the Dysphagia Disorders Survey (DDS),[9] Calis et al.[5] found a 99% prevalence of dysphagia in a group of Dutch children with a GMFCS level IV or V and an IQ < 55. These children were evaluated using a standardized mealtime observation. However, Sullivan et al. reported that almost a third of their study population with mild gross motor deficits (unilateral signs, GMFCS I and II) were identified as having feeding problems.[6] Oral motor difficulties may be linked to increased risk of choking, aspiration of food and liquids, and malnutrition affecting overall quality and the ability to fully participate in daily life.[10] In some cases, the consequences of eating, drinking, and swallowing difficulties may be fatal.[11] It is important that limitations to children's eating, drinking and swallowing are recognized as early as possible and that this information is shared effectively between parents, health professionals and other stakeholders.

Valid and reliable systems are available to classify specific aspects of everyday function in people with CP on the basis of their self-initiated movement (Gross Motor Function Classification System, GMFCS),[12] manual ability (Manual Ability Classification System, MACS),[13] and communication ability (Communication Function Classification System, CFCS).[14,15] All systems look at achievements rather than deficits and each classification system describes "performance" (people's usual activity) in five ordinal levels, rather than "capacity" (what people can do at their best). None of these systems is a performance test or even a diagnostic tool. These systems enable clinicians to communicate with families and other professionals in a uniform way about the child's functional abilities.[15]

In their systematic review, Sellers et al. identified 15 ordinal scales used to classify eating impairments in children with CP;[16] however, none met agreed quality standards of health measurement scales.[17,18] In response to this identified gap in knowledge, a new Eating and Drinking Ability Classification System (EDACS) was developed in the UK[19] with input from all stakeholders including expert professionals, people with CP and parents. This system consists of an extensive manual and an algorithm, both necessary for sufficient comprehension of eating and drinking abilities. It was designed analogous to other

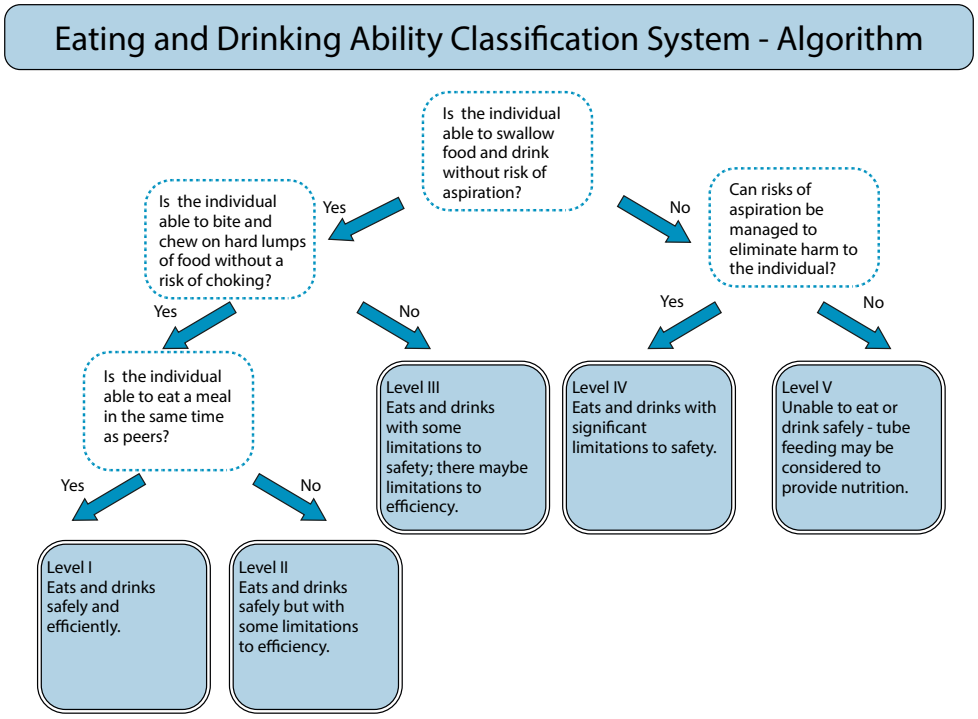

Figure 1. Clinical algorithm EDACS.

functional classification systems for people with CP (e.g. GMFCS, MACS and CFCS). EDACS can be used to classify how children and young people with CP *eat and drink* in everyday life using distinctions that are *meaningful* (Italics show the official wordings as stated in the manual itself).[20] EDACS identifies key features of *safety* (choking and risk of aspiration), and *efficiency* (time taken and loss of food from the mouth) linked with limitations to eating and drinking ability. Five distinct levels of ability are described in an ordinal scale ranging from Level I "eats and drinks safely and efficiently" to Level V "unable to eat and drink safely" (Fig. 1, the summarized algorithm). Degree of assistance required to bring *food and drink* to the mouth is described in a separate three level ordinal scale: "Independent", "Requires Assistance" and "Totally Dependent". The interrater reliability of EDACS met recognized quality standards when used by pairs of Speech and Language Therapists (SLTs) (n = 19) who classified the eating and drinking abilities of children and young people with CP they knew well (n = 100) (absolute agreement 78%; kappa = 0.72; ICC = 0.93; 95% CI 0.90–0.95).[17]

Sellers et al. also investigated the interrater reliability between parents and SLTs in order to examine the relationship between their respective viewpoints. By inviting parents to classify their children's abilities, it is possible that parents will feel empowered and that their opinions matter.[21] Differences of opinion can form the basis of discussion about the most applicable EDACS level with the recognition that parents will have better knowledge

than professionals of their child's eating and drinking abilities across a range of situations and environments. There is evidence that parents can be reliable partners in classifying their child's functional status.[15]

The objectives of this study were (1) to translate the EDACS into Dutch by a validated translation method, (2) to examine the interrater reliability of the translated EDACS among SLTs for a cohort of Dutch children and young people with CP, (3) to investigate interrater reliability between SLTs and parents in the same cohort, (4) to assess the usability of the Dutch EDACS by SLTs and parents, and (5) to examine association between the EDACS and the Dysphagia Management Staging Scale (DMSS),[9] the GMFCS, CFCS, and MACS to determine its construct validity. A strong association was hypothesized for the DMSS in contrast to a moderate association for the other classification systems. The DMSS is a five-level ordinal scale used to classify severity of feeding and swallowing problems based on management needs and health related outcomes. It is used in conjunction with the DDS as a screening and clinical assessment of swallowing and feeding function for eating and drinking in people with developmental disability.[9]

Methods

The development of the Dutch version of EDACS involved two distinct phases. The first phase consisted of translation of EDACS into Dutch. The second study phase consisted of investigating reliability, validity and usability of this Dutch version of EDACS. Written informed consent was obtained from the parents (or caregivers) and participating SLTs. This research was conducted in accordance with national and international ethics standards. The study was submitted to the Regional Hospital Human Ethics committee (registration number 2013–530).

Phase 1: Translation of the English EDACS into Dutch

First, a literature search by PUBMED on methods used to translate medical classification systems was conducted. Translation was undertaken using the method of Eremenco et al.[21] because it was considered to be thorough, practical, affordable, and used by other research groups in children's rehabilitation. The method was applied in the following steps: (1) two forward translations were undertaken by a qualified translator with medical background and one without medical background (whose native language was Dutch), (2) one version combining both translations was agreed on by both translators, (3) one backward translation was created by a qualified translator with native English, (4) three reviewers (PJ, DSn and KvH) with expert knowledge of limitations of eating and drinking associated with CP reviewed the translation process and made adjustments, (5) the English member of the research group (DSe) reviewed and made adjustments to the backward translation, and (6) final adjustments

were made by the Dutch members of the research group. The Dutch version of EDACS with a clinical algorithm can be downloaded from the website: www.EDACS.org.

Table 1: Demographics of participants included in the reliability study.

Characteristics of children and young people with cerebral palsy (*n* = 150)	***n***	**%**
Sex		
Boys	83	55.3
Girls	67	44.7
CP classification according to SCPE		
Spastic	104	69.3
Dyskinetic	8	5.3
Ataxia	1	0.7
Worster Drought	2	1.3
Mixed	35	23.4
GMFCS		
I	14	9.3
II	30	20.0
III	23	15.3
IV	51	34.0
V	32	21.3
Unknown	0	0
MACS		
I	8	5.3
II	40	26.7
III	38	25.3
IV	38	25.3
V	18	12.0
Unknown	8	5.4
CFCS		
I	20	13.3
II	29	19.3
III	27	18.0
IV	62	41.3
V	11	7.3
Unknown	1	0.7
Feeding technique		
Tube feeding	6	4.0
Oral feeding	130	86.7
Tube and oral feeding	14	9.3
Age		
Mean y	10 (4)[a]	
Median y	10 (3–19)[a]	
Characteristics of Speech and Language Therapists (*n* = 31)	***n***	**%**
Experience[b]		
< 1 y	1	3.33
1–5 y	3	10
5–10 y	7	23.3
> 10 y	20	66.7

[a]Data of age are presented as mean (SD) and median (range).
[b]Experience in working with children and young people with Cerebral Palsy. CP, Cerebral Palsy; SCPE, Surveillance of Cerebral Palsy in Europe; GMFCS, Gross Motor Function Classification System;
MACS, Manual Ability Classification System; CFCS, Communication Function Classification System, y = year.

Phase 2: Reliability, validity and usability study

Participants

Only participants (SLTs) of the last five curricula of the Pediatric Neurorehabilitation Cerebral Palsy course in the Netherlands, still working with children with CP were selected and invited to take part in the study. All SLTs were recruited by email. As recommended by Palisano et al.,[12] the SLTs were trained in using EDACS, by attending a single 3-hour training session. The training session was provided by KvH, DSn and CE. This meeting consisted of an introduction to EDACS, an explanation of the manual, and a practice session using EDACS to classify function from video recordings of four children and young people with CP whilst eating and drinking. Parents received the EDACS user manual and a separate glossary by post and were invited to participate and classify their children's eating and drinking abilities using EDACS. SLTs were asked to recruit and classify three to five children who were attending special schools and rehabilitation centers. The following inclusion criteria were: age between 3 to 21 years, diagnosis of CP, and no intercurrent illness (e.g. cold or flu) at the time of rating. Two "mealtimes" (lunch and snack) were observed at the same day to observe the child's abilities.

To include a heterogeneous group of children, it was not necessary to have established eating and drinking difficulties. Demographic information was collected from the medical record, including age, sex, CP subtype, GMFCS level, MACS level, CFCS level, and source of nutrition (tube, oral or combination). Table 1 shows the characteristics of 150 children with CP and 31 SLTs participating in this study.

Procedure

The reliability study was designed to reflect typical practice within the Dutch healthcare system. Rehabilitation teams, in the Netherlands, usually have only one SLT engaged in the treatment of a child with CP. Typically the SLT has sole knowledge of the child's eating and drinking abilities.

In this study, we evaluate the differences in scoring between pairs of two SLTs. For the interrater study the SLTs (n = 31) had two distinct functions: they classified both the eating and drinking abilities of three to five children they knew well (primary as SLT-1) as well as three to five children they had not met before and with whom they were 'unfamiliar' (secondary as SLT-2). In this way, each child was classified by a familiar SLT and an unfamiliar SLT. Furthermore, we evaluated the differences between SLT-1 and the parent(s). Parent rating was completed by one parent of each child.

All participating SLTs and parents independently classified the usual eating and drinking performance of the children with CP on EDACS. They also determined the degree of assistance required. SLTs-2 visited the children in the rehabilitation setting or special needs school they were attending. Two mealtimes (morning snack, lunchtime) were observed on the same day and all SLTs obtained access to the children's health histories. They observed

Table 2: Interrater reliability measures with use of EDACS by SLTs (*n* = 31). (a) Reliability of EDACS levels I-V, SLT-1 versus SLT-2. (b) Reliability of degree of assistance needed, SLT-1 versus SLT-2.

		SLT-2					Total
		I	II	III	IV	V	
SLT-1	I	18	8	2	0	0	28
	II	9	37	6	0	0	52
	III	0	9	12	5	0	26
	IV	0	2	9	20	1	32
	V	0	0	1	1	9	11
Total		27	56	30	26	10	149

		SLT-2			Total
		Independent	Requires assistance	Totally dependent	
SLT-1	Independent	59	3	0	62
	Requires assistance	19	25	4	48
	Totally dependent	1	2	35	8
Total		79	30	39	148

SLT-1, Speech and Language Therapist familiar with the child; SLT-2, Speech and Language Therapist unfamiliar with the child. (a) ICC 0.84, 95% CI 0.79–0.88. (b) ICC 0.85, 95% CI 0.80–0.89. The grey boxes represent absolute agreement.

Table 3: Interrater reliability measures with use of EDACS by SLTs (a) Reliability of EDACS levels I–V, SLT-1 (*n* = 31) versus parent (*n* = 81). (b) Reliability of degree of assistance needed, SLT-1 (*n* = 31) versus parent (*n* = 82).

		Parent					Total
		I	II	III	IV	V	
SLT-1	I	9	9	0	0	0	18
	II	6	15	4	0	0	25
	III	0	6	7	1	0	14
	IV	0	1	9	8	0	18
	V	0	0	1	2	3	6
Total		15	31	21	11	3	81

		Parent			Total
		Independent	Requires assistance	Totally dependent	
SLT-1	Independent	20	14	0	34
	Requires assistance	4	20	6	30
	Totally dependent	0	1	17	18
Total		24	35	23	82

EDACS, Eating and Drinking Ability Classification System; SLT-1, Speech and Language Therapist familiar with the child. (a) ICC 0.80, 95% CI 0.71–0.87. (b) ICC 0.77, 95% CI 0.66–0.84. The grey boxes represent absolute agreement.

the eating and drinking abilities 'live' (*n* = 105) or watched video clips of children engaged in usual eating and drinking routines at school (*n* = 43).

SLTs' and parents' opinions about the usability of EDACS were assessed by four questions. Both SLTs and parents were asked to rate the clarity of level descriptions and of level distinctions using a four-point scale: 'outstanding', 'good', 'moderate', or 'bad'. Also, they were asked to rate how easy it was to use EDACS using a three-point scale: 'easy', 'neutral', or 'difficult'. Finally SLTs and parents were asked about the time needed to complete the EDACS (in minutes). All questionnaires were distributed and collected by a gatekeeper.

To determine the construct validity of EDACS, SLTs also classified children using one of the five levels of the DMSS. The DMSS consists of variables selected because they are sensitive indicators of the presence and functional adequacy of swallowing and feeding disorders in people with developmental disabilities. The level of the DMSS was determined by observation and on the basis of available medical information.[9]

Statistical analysis

Interrater reliability was analyzed using Intraclass Correlation Coefficient (ICC) with a two-way random model for absolute agreement (single measure) and by linear weighted kappa kW. Weighted kappa was added as an indication of chance corrected agreement because it gives different weights to disagreements according to the magnitude of the discrepancy. For example, a rating difference of two levels is more serious than a difference of one level. Values for ICC and kW were interpreted following Cicchetti et al.: reliability is poor with an ICC < 0.40, fair between 0.40–0.59, good between 0.60–0.74, and excellent between 0.75–1.00.[22] Terwee et al. recommended ICC > 0.70 as a minimum standard for reliability in a sample size of at least 50 patients.[17] A Wilcoxon signed-ranks test was performed to evaluate differences within paired scores of SLT-1 and a parent.

The associations of EDACS level with degree of assistance required, as well as with DMSS, GMFCS, CFCS, and MACS, were calculated using Kendall's tau-b. Descriptive analysis was used to report the usability of the EDACS system. Missing values were considered as missing at random. For all statistical tests, the level of significance for two-tailed p-values was set at ≤ 0.05. Point estimates are presented with their 95% confidence intervals (CIs). Statistical analyses were carried out using SPSS 20.0 for Windows.

Results

Participants

An invitation to participate was sent by email to SLTs who met the inclusion criteria to participate in the initial meeting for the study (approximately 80 SLTs). Thirty-one of the 38 SLTs who attended this initial meeting agreed to participate. In 16% of the cases, the familiar SLTs knew the child's eating and drinking abilities through group therapy; in the

remaining cases, the familiar SLTs knew the child's abilities from individual therapy in the past or present.

Reliability

The level of agreement between SLTs-1 and SLTs-2 was excellent. They agreed on EDACS level in 96 out of 149 children (ICC 0.84; 95% CI 0.79–0.88; Kw = 0.71); as reflected in Table 2. One child was scored only by SLT-1 and the parent. When pairs of SLTs scored the degree of assistance required, a good interrater reliability was achieved (ICC 0.85; 95% CI 0.80–0.89; Kw = 0.77). In five children, there was a twolevel difference between SLT-1 and SLT-2. When SLTs disagreed by more than 1 level, this seemed related to omission or misinterpretation of information concerning medical notes, respiratory function or changed food consistencies between the two observation moments influencing the scoring of EDACS level.

Eighty-one children (54%) were rated by their parents and SLTs for EDACS level, and 82 children (55%) were categorized on degree of assistance needed (see Table 3). The level of agreement was 0.80 (95% CI 0.71–0.87; k_w = 0.61) versus 0.77 (95% CI 0.66–0.84; k_w = 0.64) for the degree of assistance required. The Wilcoxon signed rank test indicated that the median SLT scores for EDACS level were statistically higher than the median parent scores (z = -1.94, p = 0.052), i.e. SLTs scaled the child as having more problems with eating and drinking than the parent of the child (Table 3). When comparing degree of assistance needed, SLTs scored the children as needing less help for eating and drinking than parents did (z = -3.00, p = 0.003).

Validity

There was a significant and positive correlation between EDACS level and degree of assistance required for eating and drinking (Kendall's tau-b 0.69, $p < 0.001$). There was a strong association of EDACS level with DMSS level (Kendall's tau-b 0.81, $p < 0.001$), whereas the other associations were only moderately positive (GMFCS: Kendall's tau-b 0.60, $p < 0.001$; MACS: Kendall's tau-b 0.48, $p < 0.001$; CFCS: Kendall's tau 0.50, $p < 0.001$).

Usability

SLTs and parents were asked to judge the usability of EDACS. The questions assessing usability of EDACS showed that 23% of the EDACS classifications made by SLTs-1 and 2 (70/300) were categorized as 'outstanding' regarding the understanding of the user instructions, 73% (220/300) were categorized as 'good' and 3% (10/300) as 'moderate'. Of the parents, 30% (24/81) understood the instructions 'outstanding', 65% (53/81) 'good', 3% (2/81) 'moderate', and 3% (2/81) 'bad'. When the SLTs classified an unfamiliar child, in 34–39% of the cases, the SLTs considered choosing between levels to be 'easy', in 49–51% of the cases 'neutral', and in 10–14% of the cases 'difficult'. In two cases, the SLTs did not answer this question. Similar to these results, 47% percent of the parents thought choosing between levels to be 'easy',

43% found it 'neutral', and 10% found it 'difficult'. The mean time needed to classify a child on the EDACS was 13 minutes for SLTs-1 (SD 7.9 range 1–30), 15 minutes for SLTs-2 (SD 8.9 range 2–60), and 16 minutes for parents (SD 8.1 range 1–35).

Discussion

The content of EDACS has been successfully translated into Dutch following a thorough, validated translation process. The key features of safety and efficiency of eating and drinking ability expressed in five distinct levels were considered meaningful and feasible by parents and SLTs working within the Dutch healthcare system. EDACS enables clear and efficient communication about a child's eating and drinking skills between professionals and between professionals and parents.

There were only slight differences in interrater reliability outcomes among SLTs obtained in this study (ICC 0.84) compared to the original study by Sellers et al. (ICC 0.93). Both results are judged as statistically 'excellent' following the interpretation of Cicchetti.[22] Sellers et al.[19] assessed reliability of EDACS when used by pairs of SLTs who were both familiar with the child's usual eating and drinking performance. In this study, eating and drinking abilities were classified by one SLT familiar with the child's current feeding abilities, and one SLT who was unfamiliar with the child's feeding abilities. Videos, live observations, and medical records were used by the latter SLTs (SLTs-2) to classify eating and drinking ability. It is possible that in some cases the 'unfamiliar' SLTs (SLTs-2) did not have enough background information to be able to classify all aspects of eating and drinking. This might explain the slightly lower SLT interrater reliability in the present study compared to Sellers' study. Another explanation may be found in the larger number of subjects used in our study and greater (between subjects) variability of their eating and drinking abilities. From these findings, it can be concluded that eating and drinking ability can be classified by SLTs who are 'familiar' or 'unfamiliar' with the child from direct observation or from video recording.

The ICC value of 0.8, when EDACS is used by SLTs as well as parents, shows that this instrument can be reliably used by an informed parent. This supports the idea that parents should be considered as serious discussion partners. There is a trend for parents to classify their child on a lower EDACS level, i.e. greater abilities with eating and drinking, when compared with the opinion of the SLT. Possible explanations for this finding are that parents may be less aware of risk factors for inefficient or unsafe eating and drinking, or that parents may be more tolerant of risks to support their child to function at the edge of his/her abilities. SLTs may limit exposure to risks in a school or clinic setting for safety reasons. For the degree of assistance required during eating and drinking, parents reported their child to be in need of more help than the SLTs did. Parents may provide their child with more help when eating and drinking for practical reasons such as speeding up the time taken to finish a meal, whilst in a school setting when given enough time, a child may be able to eat and drink independently.

The moderate positive association between EDACS and GMFCS highlights that measures of gross motor function will not be sufficient to predict a child's eating and drinking ability. The moderate positive association between a child's ability to use his/her hands (MACS) and level of assistance needed to bring food and liquids to the mouth also highlights that MACS as a measure of hand function is insufficient to predict levels of dependency at mealtimes. The strong correlation between EDACS and DMSS reflects the construct validity of EDACS. However, the DMSS (linked to DDS assessment) can be used only by qualified clinicians in people with developmental disabilities. It is a validated scale where the level of the swallowing and feeding disorder is determined rather than the eating and drinking ability of the child with CP.[9] For scaling, the information from a parent questionnaire is used. It is not suitable for use by parents to convey their ideas about the child's eating and drinking ability. Functional classification systems have arisen from models of healthcare based on family centered practice including collaborative teamwork with parents. The EDACS, along with the other functional classification systems for CP, enables parents, clinicians and researchers to communicate clearly with one another.[23] In this respect, our findings support the complementary use of DMSS and EDACS in clinical practice.

Overall, this study shows that EDACS is reliable and valid when used by experienced SLTs, both 'familiar' and 'unfamiliar' with the child and also when used by parents. For other healthcare professionals, the concepts of EDACS should be known thoroughly for adequate use of this classification system in partnership with parents. The usability study showed fairly good results in differentiating between levels, and also shows room for improvement, considering that 10-14% of users of the EDACS (SLTs and parents) experienced difficulties differentiating between the various levels. An E-learning module is beneficial in this respect.

Limitations

Only SLTs experienced in working with children with CP participated in the present study. In daily practice, not all SLTs will meet this standard, which is a limitation of our study. In addition, SLTs only observed lunch and snack times at school and did not observe usual mealtimes at home. They were aware of, but did not observe, all the different food texture choices made at home to ensure mealtime safety and efficiency within the context of the child's environment away from school. This emphasizes the need for discussing a child's eating and drinking ability with parents in routine care, and the utility of EDACS to support this. It should be noted that selection bias may have influenced the observed interrater reliability and usability. For instance, parents whose native language was not Dutch were not included in our study.

EDACS can be used to describe limitations on someone's overall eating and drinking ability arising from CP. The gross categorical distinctions between EDACS levels can be insensitive to subtle features of someone's eating and drinking ability. For example, some children show greater limitations in eating and drinking ability than one may expect when only considering oral motor capacities because of behavioural issues or hypersensitivity of

the oral area. A child's lack of experience or exposure to more challenging food textures or fluid consistencies may also suggest greater limitations to their eating and drinking ability.

Future perspectives

EDACS has the potential to address questions concerning the prevalence of limitations in eating and drinking abilities of children with CP at the population level. Also, the association of eating and drinking ability with other areas of functional ability (including gross motor function, speech and hand function) can be addressed as well as weight/growth data and functional prognosis. EDACS provides professionals with a means to describe observations of safety and efficiency linked to eating and drinking. EDACS highlights and points to the need to explore the difference between the eating and drinking 'performance' (usual activity) and 'capacity' (what a child can do at his/her best). As with the GMFCS, it is possible for eating and drinking difficulties to be identified and linked to different EDACS levels with the aim to support clinical management.

There is limited data concerning time related changes in eating and drinking abilities in people with CP. It is therefore uncertain how frequently children's eating and drinking abilities should be reclassified using EDACS. Prospective longitudinal studies to examine the stability of EDACS levels over time are yet to be conducted. Longitudinal studies using the GMFCS and MACS demonstrate that individuals with CP usually remain stable over time and that, when there is change, it is no more than one level.[24,25] Yet, uncertainties remain with regard to the natural course of eating and drinking difficulties in CP. Some clinicians expect that, over the years, a child may gradually be able to eat more challenging textures, use more types of utensils, and become more independent whilst eating and drinking.[9] However, as children with CP reach puberty, risk of aspiration may increase; not only by changes in nutritional needs or increase in scoliosis, but also due to anatomical and physiological changes of the oropharynx.[7] Consequently, oral motor growth and changes in posture might lead to a different EDACS level which would warrant repeated assessments. There is also clinical utility in investigating the correlation between nutritional status and EDACS level with the potential for EDACS to identify an increased risk of malnutrition due to limitations in eating and drinking abilities.

Conclusion

In conclusion, the Dutch EDACS is the first reliable, valid, and easily applicable tool to classify functional eating and drinking abilities in children with CP when used by experienced SLTs or parents. It will enhance the communication concerning eating and drinking abilities of these children among professionals and parents. It is analogous to other functional classification systems (GMFCS, MACS and CFCS). Use of EDACS may increase the awareness of safety and efficiency of eating and drinking ability in children with CP amongst different stakeholders.

It has the potential to form the basis for discussions with parents and other caregivers about the safety and efficiency of children's eating and drinking abilities.

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5

CHAPTER 5

Accurate assessment of drooling severity with the 5-minute Drooling Quotient in children with developmental disabilities

K. van Hulst
R. Lindeboom
J.J.W. van der Burg
P.H. Jongerius

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Abstract

Aim: The aims of this study were to examine whether objective measurements of the 10-minute drooling quotient (DQ10) and the 5-minute drooling quotient (DQ5) are interchangeable; to assess agreement between the measurements and their accuracy in classifying drooling severity; and to develop a time-efficient clinical assessment.

Method: The study cohort included 162 children (61 females, 101males;mean age 11y 6mo, SD 4y 5mo, range 3y 9mo–22y 1mo) suffering from moderate to profuse drooling. One hundred and twenty-four had cerebral palsy and 38 had other developmental disabilities. Seventy-four of the participants were ambulant and 88 non-ambulant. The original DQ10 was recalculated into a 5-minute score (DQ5). Assessments were undertaken while the participants were in a rest situation (DQ^R) and while they were active (DQ^A). Agreement in scores was quantified using intraclass correlations and Bland–Altman plots. To classify drooling, area under the receiver operating characteristic curve analysis was used to compare accuracy of the DQ10 and DQ5 at rest and during activity.

Results: Agreement between $DQ10^A$, and $DQ5^A$, and between $DQ10^R$ and $DQ5^R$ was high (intraclass correlation coefficient > 0.90). Moderate agreement existed between DQ^A and DQ^R. DQ^A scores were more accurate in classifying children's drooling behaviour. For $DQ5^A$, a cut-off point of 18 or more (drooling episodes ⁄ observation time) might indicate 'constant drooling'.

Interpretation: The DQ10 and DQ5 can be used interchangeably. DQ^A is most discriminative for drooling severity. For evaluating treatment efficiency the cut-off point can be used. For clinical and research purposes, the DQ5 is time efficient and cost saving while validity, and intrarater and interrater reliability are preserved.

Drooling is defined as the unintentional loss of saliva from the mouth.[1] In children with cerebral palsy or other developmental disabilities, drooling may persist after toddlerhood as a result of impaired muscle control of the tongue, lips, or throat; malocclusion; disturbed swallowing; inability to maintain an upright position of the trunk and head; or the incomplete development of an automatism to swallow saliva.[2,3] The severity and impact of drooling are assessed by both subjective and objective measurements. Subjective scales such as the Drooling Rating Scale, the Drooling Frequency and Severity Scale, the Visual Analogue Scale (VAS), and the Drooling Impact Scale[4,5] are completed by patients or their caregivers, who give their qualitative and quantitative impression of the severity and impact of drooling.

Although Blasco[6] stated that the 'ultimate test of whether treatment will be continued or not is whether it makes the caregiver's life easier and their child's life improved', evidence for effective treatment cannot be derived from satisfaction scores alone. An additional objective measure may be supportive, both in effect evaluation and in decision-making for intervention. Objective measures related to drooling include salivary flow measures and direct observations of saliva loss (e.g. counts of saliva drops) from the mouth.[4,7] In this study we focus on the objective measurement of drooling severity: the drooling quotient as originally proposed by Rapp[8] and modified thereafter.[4,9] The drooling quotient represents a semiquantitative, direct observational method that evaluates drooling by measuring leaked saliva from the mouth (so-called anterior drooling). In its original form, Rapp and Bowers[10] used a 'teacher prompt device' to obtain measurements of drooling in moment-by-moment sampling observations in the classroom. Forty randomly evoked bleeps over a 10-minute period ordered the teacher to score if the child drooled or not. Drooling was defined as a string of drool, either continuous or falling at the time of the cue. The authors found an interobserver agreement of 99%. Reddihough et al.[11] redesigned the drooling quotient to a partial interval time sampling observation of drooling at 15-second intervals over a 10-minute period. Drooling was defined as 'new saliva present beyond the lip margin', to avoid double counting. In a controlled clinical trial by Jongerius et al.,[4] the drooling quotient was applied in a standardized setting during two observation sessions of 10 minutes. Drooling was scored positive if during a 15-second interval new saliva was present on the lip margin or dropping from the mouth or chin area. Because drooling severity may vary significantly depending on the level of activity or the ability to focus attention on the need to swallow, each child was observed both at rest ($DQ10^{R}$) and during an activity ($DQ10^{A}$) that demanded a higher level of concentration or physical effort.[4,12]

Although the 10-minute drooling quotient (DQ10) has been used to evaluate the effect of treatment for drooling, there are no validity and reliability data available for the DQ10. In addition, the procedure is rather costly and timeconsuming, taking two periods of 10 minutes (during activity as well as rest). From a clinical point of view, it would be valuable to reduce scoring time.

The aim of this study was to investigate whether the validity and reliability of drooling severity measurement would be preserved at a 5-minute scoring time. We

hypothesized that results from a 5-minute drooling quotient (DQ5) and DQ10 would be interchangeable for children with moderate to profuse drooling. In addition, we wanted to identify a clinically meaningful number of drooling episodes to support decisionmaking for intervention and measure response to these interventions.

METHOD

Participants

This study was part of a project in which the effectiveness of either botulinum toxin type A (BoNT-A) injections into the salivary glands or surgery to reduce salivary flow was evaluated.[4,13,14] All participants attended the multidisciplinary outpatient drooling clinic at the Radboud university medical center, Nijmegen, the Netherlands, between 2003 and 2010. For this study, we included 162 children with moderate to profuse drooling (i.e. Teacher Drool Scale* scores 3 and higher[15]). Children were included if complete data for baseline drooling measurements and repeated drooling measurements 8 weeks after intervention were available.

Patient characteristics including some drooling measurement results are summarized in Table 1. One hundred and thirty-eight children received injections of BoNT-A to the salivary glands, 17 children had saliva control surgery, six children received behaviour therapy, and one child underwent an adenoidectomy. Sixty-one females and 101 males (age range 3y 9mo–22y 1mo; mean age 11y 6mo, SD 4y 5mo) were enrolled. Among them, 74 children were ambulant and 88 children were wheelchair bound. Diagnosis comprised cerebral palsy (*n*=124) and developmental disability (*n*=38), mainly as part of a syndrome or unexplained developmental delay.

Written and oral informed consent was obtained from either the children or their parents or caregivers. The research was conducted in accordance with national and international ethics standards. The Regional Committee on Research Involving Human Subjects approved the study. Exclusion criteria were enrolment in another medical study, use of drugs interfering with saliva secretion, and a previous surgical procedure for saliva control.

*Teacher Drool Scale: 1, no drooling; 2, infrequent drooling, small amount; 3, occasional drooling, on and off all day; 4, frequent drooling, but not profuse; 5, constant drooling, always wet.

Table 1: Characteristics of the study group (*n*=162) and drooling measurement results.

Characteristics	*n*	%
Sex		
Male	101	62
Female	61	38
Main diagnosis		
Cerebral palsy	124	77
Other developmental disability	38	33
Mobility		
Ambulant	72	44
Non-ambulant	88	54
Unknown	2	2
Intellectual impairment Developmental age		
<4y	91	56
4–6y, IQ<70	22	13
4–6y, IQ>70	7	4
>6y	38	24
Missing	4	3
Intervention		
Botulinum toxin A injections	138	85
Saliva control surgery	17	10
Behaviour therapy	6	4
Other	1	1
Drooling measurements	**Mean**	**SD**
VAS	66	23.94
Total salivary flow rates	0.62	0.56
DQ versions		
$DQ10^A$	20.07	16.77
$DQ10^R$	14.04	13.51
$DQ5^A$	20.28	18.12
$DQ5^R$	14.54	15.00

Mean age of study cohort 11 years 6 months (SD 4y 5mo). VAS, Visual Analogue Scale; DQ, drooling quotient; $DQ10^A$, 10-minute drooling quotient during activity; $DQ10^R$, 10-minute drooling quotient at rest; $DQ5^A$, 5-minute drooling quotient during activity; $DQ5^R$, 5-minute drooling quotient at rest.

Measurement procedures

All children were assessed by two trained speech therapists (Karen van Hulst and Sandra de Groot) at baseline and follow-up. Follow-up was at 8 weeks after treatment when the children attended the outpatient clinic. If possible, the sessions were videotaped. From the completed assessment (162 children) we randomly selected baseline (*n*=86) and follow-up (*n*=76) data to create a study sample with a high degree of heterogeneity. All measurements took place under standardized conditions in the morning at least 1 hour after mealtime. During the drooling quotient 'rest' condition, the child was allowed to watch television, sitting upright in his or her own (wheel)chair and prohibited from talking. The kind of activity performed during the drooling quotient 'activity' condition was adapted to the child's cognitive and movement abilities and interest: for example, some children built blocks for dual tasking while others used their electronic communication device.

In one morning session, the measurements occurred in the following order: (1) $DQ10^A$, (2) salivary flow measure of the submandibular and parotid glands,[12,16] (3) visual analogue scale scores of severity as perceived by the parents (0=no drooling, 100=excessive

drooling), (4) Drooling Severity and Frequency Scale scores, as judged by the parents or caregivers, and (5) $DQ10^{R}$. Before starting the drooling quotient assessment, saliva was wiped off the chin, and any food that remained in the mouth was removed. Drooling was defined as a drip of new saliva present on the lip margin or a string of saliva dropping from the mouth or chin area. During 10 minutes, for every interval of 15 seconds, the presence or absence of drooling was determined. The drooling quotient was expressed as a percentage of observed drooling episodes and the total number of intervals.

Reliability of the assessments

An intrarater and interrater reliability design with four raters and 10 video clips of the $DQ5^{R}$ and $DQ5^{A}$ were used to assess reliability of the DQ5 version during rest and activity. The raters were selected on the basis of their broad experience in assessing the target group. All raters received a 3-hour training session and scored the video clips at two different time points separated by at least 3 weeks. A wide selection of available video clips was recorded with children in different mobility classes, at different developmental ages, with different diagnoses, and different measurement moments.

Statistical analysis

DQ10 measurements during rest and activity were recalculated into DQ5 by taking the first 5 minutes of the scoring time; instead of 40 episodes of 15 seconds, the first 20 intervals of 15 seconds were judged. Agreement between the DQ10 and DQ5 during activity and at rest was quantified by the intraclass correlation coefficient (ICC), two-way random, single measure. For the evaluation of agreement, the classification of Landis and Koch[17] was used. The magnitude of the DQ5 deviations from the DQ10 was examined by the Bland–Altman method and included the calculation of limits of agreement.[18] Interrater reliability of the assessments from the video clips was evaluated using the ICC two-way random model for absolute agreement, single measure. Intrarater reliability was calculated by a two-way mixed model with the raters considered as a fixed effect, also single measure.

The criterion validity of the drooling quotient scores was evaluated by the relation with the parent's evaluation of drooling frequency according to the four-point classification of drooling frequency by Thomas-Stonell and Greenberg,[19] considering 'frequently drools' and 'constantly drools' as 'constant drooling' and 'never drools' and 'occasionally drools' as 'on-and-off drooling'. The overall accuracy of all drooling quotient versions in correctly classifying children as 'constant drooling' was evaluated using receiver operating characteristic curve analysis. The area under the receiver operating characteristic curve (AUC) may range from 50% (meaning no accuracy of the drooling quotient score to classify correctly) to 100% (meaning excellent classifying accuracy). We considered an AUC of at least 0.7 as fair, 0.8 as good, and 0.9 as excellent.[20]

The optimal drooling quotient cut-off points were determined by applying the Youden method (% sensitivity + % specificity) -100),[21] which minimizes the number of false-

positive and false-negative misclassifications. We also calculated the Pearson's correlation of the individual drooling quotient versions with the VAS for drooling severity. Furthermore, the correlation was calculated between all the drooling quotient versions and the scores of total salivary flow measured by the dental swab method.[4]

For all statistical tests, the level of significance for two-tailed *p*-values was set at ≤ 0.05. Point estimates are presented with their 95% confidence intervals (CIs). All analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

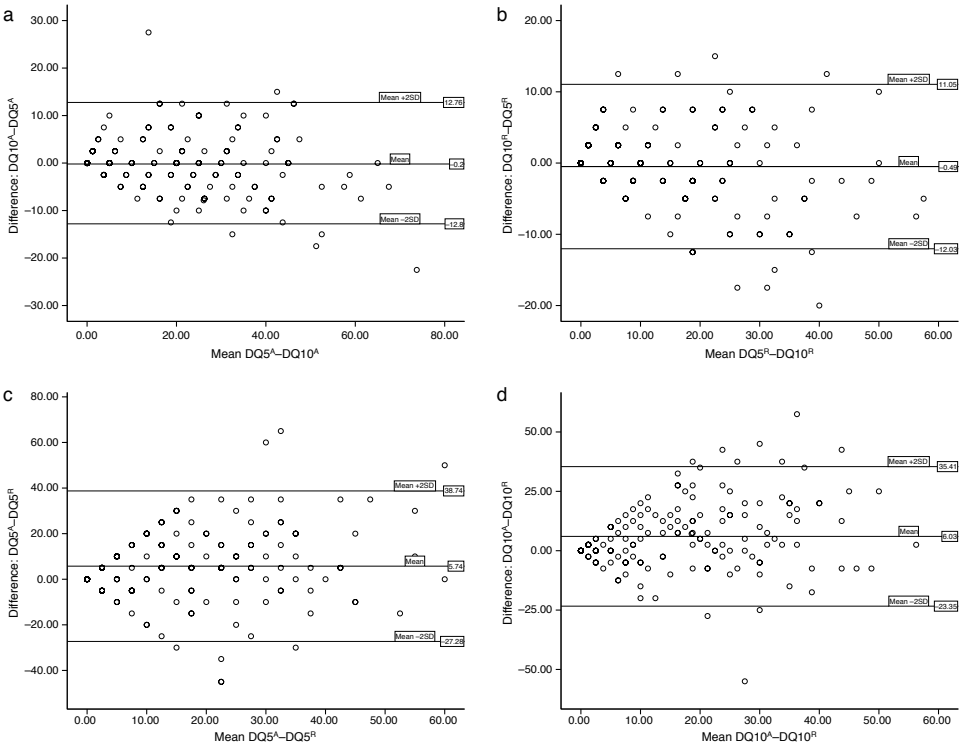

Figure 1. Intraclass correlation coefficients (ICCs) and Bland–Altman plots for the agreement between different drooling quotient versions. (a) $DQ10^A$–$DQ5^A$ (ICC 0.93; 95% confidence interval [CI] 0.90–0.96). (b) $DQ10^R$–$DQ5^R$ (ICC 0.92; 95% CI 0.89–0.94). (c) $DQ5^A$–$DQ5^R$ (ICC 0.53; 95% CI 0.42–0.64). (d) $DQ10^A$–$DQ10^R$ (ICC 0.51; 95% CI 0.38–0.63).

RESULTS

Figure 1 presents the ICC values and Bland–Altman plots for the agreement between the different drooling quotient versions. The ICCs for agreement between $DQ10^A$ and $DQ5^A$ and the agreement between the $DQ10^R$ and $DQ5^R$ were over 0.90, indicating a high level of agreement. The ICCs for agreement between the DQ^A versions and the DQ^R versions were 0.50 and 0.53 respectively, representing a moderate agreement. The mean difference between

$DQ10^A$ and $DQ5^A$ scores -0.2; SD 6.39) indicates a small negligible systematic error. Six out of 162 deviation points (3.7%) were outside the 2SD limits of agreement. Two participants had much more saliva production and high DQ scores during the last 5 minutes of the DQ10 and another four participants had more saliva dripping during the first 5 minutes, explaining most of the deviation outside the 2SDs. An almost similar number of outliers (6.8%) were registered from the Bland–Altman DQ^R plot. Here, again, the mean difference -0.5; SD 5.8) showed a small and negligible systematic error. The Bland–Altman plots for the DQ^A and DQ^R comparisons reflected the lower agreement. The systematic error for the $DQ10^A$ and $DQ10^R$ comparison was 6.03 (SD 14.7) and for the $DQ5^A$ and $DQ5^R$ comparison was 5.74 (SD 16.5). The Bland–Altman plots for the $DQ10^A$ and $DQ10^R$ showed broad limits of agreement (between 34.8 and 122.8). Thus, the activity measurement may be 34.8 percentage points above or 22.8 percentage points below the rest situation.

The accuracy of the different drooling quotient versions to correctly classify children as 'constant drooling' is presented in Table 2. Thirty-two children (19.8%) were classified as drooling' 'on-and-off' and 130 children (80.2%) were classified as drooling 'constantly'. The accuracy of the $DQ5^R$ (AUC=0.69) and $DQ10^R$ (AUC=0.73) was lower than that of the $DQ5^A$ and $DQ10^A$ (both AUC=0.80).

Using the Youden method, the drooling quotient cut-off point with a minimum risk of false-positive or false-negative classifications was lower for DQ10 (DQ^A 11 points and DQ^R 14 points) than for DQ5 (DQ^A and DQ^R both 18 points). The correlations between the drooling quotient versions with the VAS scores and the salivary flows are summarized in Table 3. The Pearson's correlations for the VAS ranged from 0.35 to 0.46. The correlations for the salivary flows ranged between 0.26 and 0.31. The correlations between the VAS and the activity versions of the drooling quotient, $DQ10^A$ and $DQ5^A$, were higher than for the rest versions. The correlations with salivary flow were similar for the activity and rest versions of the drooling quotient.

The ICC for the interrater reliability of the DQ5 scores as obtained from the video assessments was 0.95 (95% CI 0.85–0.99). Intrarater ICCs for the four raters were 0.91 (95% CI 0.67–0.98), 0.86 (95%CI 0.55–0.96), 0.95 (95% CI 0.80–0.99) and 0.91 (95%CI 0.67–0.98), all representing good reliability.

Table 2: Accuracy of the different drooling quotient activity and rest version.

DQ version	AUC (95% CI)	Youden cut-off	Sensitivity	Specificity
$DQ5^A$	0.80 (0.73–0.88)	18	0.61	0.75
$DQ5^R$	0.69 (0.60–0.78)	18	0.45	0.87
$DQ10^A$	0.80 (0.72–0.88)	11	0.72	0.81
$DQ10^R$	0.73 (0.63–0.82)	14	0.49	0.87

DQ, drooling quotient; AUC, area under the receiver operating characteristic curve; CI, confidence interval; $DQ5^A$, 5-minute drooling quotient during activity; $DQ5^R$, 5-minute drooling quotient at rest; $DQ10^A$, 10-minute drooling quotient during activity; $DQ10^R$, 10-minute drooling quotient at rest

Table 3: Correlation coefficients for drooling quotient versions with the Visual Analogue Scale (VAS) and total salivary flow rate.

	Pearson's *r* (95% CI)
VAS[a]	
$DQ5^A$	0.45 (0.32–0.58)
$DQ5^R$	0.35 (0.21–0.49)
$DQ10^A$	0.46 (0.33–0.59)
$DQ10^R$	0.38 (0.24–0.52)
Total salivary flow rate[b]	
$DQ5^A$	0.26 (0.11–0.41)
$DQ5^R$	0.28 (0.13–0.43)
$DQ10^A$	0.27 (0.12–0.42)
$DQ10^R$	0.31 (0.16–0.46)

[a]VAS (0=no drooling, 100=excessive drooling).
[b]Flow submandibular glands + flow parotid glandsmeasured during 5 minutes according to the swab method.
CI, confidence interval.

DISCUSSION

The drooling quotient is a reliable and valid objective procedure to measure drooling severity. Our results show that, without loss of overall accuracy, the original DQ10 can be replaced by the DQ5 during the activity as well as rest observations. The agreement between the original drooling quotient and the shorter 5-minute version was almost perfect. The observed error was random and the number of outliers acceptable for the observation during activity as well as rest. The limits of agreement were all within 10%, which represents an acceptable random error. The interrater and intrarater reliability of the DQ5 in children with moderate to profuse drooling was excellent. In this respect, clear video clips and the work of well-trained raters may have been helpful. The Youden index of the cut-off score of 18 is a function of sensitivity and specificity and is a commonly used measure of classification of effectiveness of a cut-off point. This index is lower for the $DQ5^A$ (53 vs 36) than for $DQ10^A$, indicating that a higher misclassification rate can be expected with the 5-minute version when using that cut-off. The overall accuracy (AUC) of the drooling quotients in the detection of children with 'constant' drooling behaviour was in both cases 0.80 and therefore good. For reliable assessments with the DQ5, the assessments should be

carried out under standardized conditions. This is an important prerequisite: the results of the DQ5 will be reliable only if the natural variation in saliva flow rates across daily situations (for instance while eating, at rest, etc.) are minimized. For clinical practice, however, setting up a DQ5 assessment probably exceeds 5 minutes because of preparation time and data processing, but we still argue that 5 minutes less than using the DQ10 constitutes a notable reduction in assessment time.

Drooling quotient registrations during activity were more accurate than the rest versions in correctly classifying children's drooling status. The $DQ5^{A}$ appears to be the measure of choice for use in clinical practice and research. Although the need to tailor the activity to the child's cognitive and movement abilities introduces some variability in measuring the DQ^{A}, this individualized approach was assumed to be a valid way to represent drooling severity in daily life activities. Children in our study cohort drooled more frequently during strenuous activities demanding a high motor performance and cognitive level than during rest situations. This can be explained by insufficient attention given to swallowing during activities. The Pearson's correlations, reflecting the association between the VAS (subjective assessment) for perceived drooling severity, were also higher for the DQ^{A} measurements than for the rest version. Although the DQ^{A} seemed more discriminative than the DQ^{R}, for clinical purposes the speech therapist might want to use both versions to direct the choice for intervention. For instance, in children drooling both at rest and during activities, the oral motor intervention should start during a rest situation; whereas for children who mainly drool during activities, intervention should start with promoting oral motor control during dual tasks.

Although the DQ10 can be replaced by the DQ5 in children with moderate to profuse drooling, we have to be cautious in generalizing this conclusion to drooling assessment in all children with slight to profuse drooling problems. Perhaps the frequency and occurrence of drooling episodes in children with minor drooling cannot be validly assessed during 5-minute trials. For now, it remains unknown if the DQ5 is discriminative for children with infrequent and slight drooling.

With respect to saliva, the normal situation is not to drool, reflecting a drooling quotient of zero. All our patients drooled to some extent. The subjective measurements of parents with regard to their child's drooling problem is important but should be supported by more objective measurements, especially in children with minor drooling problems. Clear cut-off points may be useful in clinical decision-making. In this study, the drooling quotient cut-off point was estimated based on the individually meaningful finding of 'constant drooling' or 'on-and-off drooling'. The cut-off point reflects the best balance for classifying children according to their drooling status. For clinical decision-making, our results suggest the use of a DQ5 cut-off point of 18 or higher as 'constant drooling', irrespective of whether the child is active or at rest. The cut-off point of 18 means 3.6 out of 20 drooling episodes of 15 seconds x 100. A cutoff point could serve as a 'rule of thumb' for decisionmaking in drooling treatment. A drooling quotient of 18 or higher means that the drooling problem is at least frequent and/or has not been not satisfactorily resolved by previous treatment.

This cut-off point may be useful in deciding whether intervention is needed. Children with a drooling quotient of less than 18 may be eligible for a more conservative intervention, such as oral motor training. In case of a higher score (drooling quotient > 18) other interventions, such as behaviour therapy, BoNT-A injections, or surgery, may be the therapy of choice. Analysing the data at group level, this cut-off point appears reasonable as the mean DQ5^{A} at baseline was 26 points, decreasing to 14 points at follow-up. However, in clinical practice, the drooling quotient cut-off point should not be rigidly applied as the only variable. In addition to subjective and objective measurements, such as the drooling quotient, one should seriously consider the impact of drooling on the child and his or her environment, hour-to-hour and day-to-day variability in drooling, and the medical history of the child as well as the outcome of multidisciplinary decision-making. The individual patient may require a flexible approach and deviation of the chosen drooling quotient threshold value should be considered from case to case in a drooling team setting. Future research should reveal the applicability of the cut-off point.

Although drooling severity varies from day to day, and sometimes from hour to hour, and across daily life situations, there is a need to quantify the drooling frequency and severity, and its impact on the quality of life of children with drooling and their carers.[14,22] The subjective opinion of parents on drooling severity and its impact, as measured by the VAS, the frequency and severity scale according to Thomas-Stonell and Greenberg,[19] the Drooling Impact Scale, and parent questionnaires,[5,22] is considered to be of utmost importance in evaluating treatment outcome. The DQ5 is measured over a brief period and gives a reliable outcome of the drooling severity. Following good clinical practice, it is particularly important to pair these measurements with the results of subjective tools that assess the impact of drooling on patient and caregiver daily life.

In recent research, little attention has been given to objective measurement methods for drooling. In addition, Parr et al.[23] found that very few paediatricians in the UK use standardized methods of measuring the effectiveness of medications, or their adverse effects, as part of their management of drooling in children. Several methods of quantifying salivary flow or the amount of saliva loss are available, such as using collection units,[24,25] weighing bibs,[5,22] or using cotton dental rolls to measure saliva flow.[4] The development of valid and reliable direct measurement tools for anterior drooling is still a challenge in research and clinical practice. The results of the Pearson's correlation of the drooling quotient versions with the VAS and the total salivary flow rate show a weak relationship, suggesting that drooling quotient cannot be replaced by the subjective VAS or an objective saliva flow measurement.

We argue that the drooling quotient is a valuable, additional, objective, semiquantitative observation tool that provides a representative measure of anterior drooling. The DQ5^{A} modification is time saving and might reduce costs without affecting the accuracy of objective drooling measurements. To our knowledge, this is the first study on the subject of drooling which suggests the use of a cut-off point to guide clinical decision-making.

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Part two

Towards a personalized approach to the treatment of drooling


6

CHAPTER 6

Evidence-informed management of sialorrhea in children and youth with cerebral palsy

A. Hughes
K. van Hulst
J.J.W. van der Burg
J. Parr
L. Pennington
D.S. Reddihough
L. J. Glader

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Abstract

Drooling, or sialorrhea, is a common problem among both children and adults with cerebral palsy (CP), with an approximate prevalence rate of 40%. There are numerous complications related to anterior and posterior drooling ranging from psychosocial impact to significant morbidity from chronic aspiration. Multiple interventions aimed at reducing or eliminating drooling have been described, however there has been no clear consensus on which are most effective. The objective of this narrative review is to summarize the published data and provide a comprehensive evidence-based overview of drooling management in children and youth with CP, from birth to age 25. While the emphasis in this paper is on individuals with CP, we have highlighted inclusion of other neurodisabilities when necessary to provide evidence of a particular treatment modality. A review of the literature review included all levels of evidence to best contextualize and guide the full range of potential clinical treatment interventions, including: oral motor and behavioral interventions, oral appliances, pharmacologic interventions, chemodenervation with botulinum toxin, and surgical options. A total of 339 articles were identified and 132 articles met the classification criteria for inclusion. Articles were graded according to American Academy of Neurology guidelines. Highest level evidence was found for pharmacologic interventions, particularly glycopyrrolate and scopolamine, and salivary botulinum toxin.

Introduction

Drooling, or sialorrhea, is a common problem among children and young adults with cerebral palsy (CP). Drooling occurs when an individual's ability to control and swallow oral secretions is limited. Its prevalence is thought to be around 40% with a slightly increased occurrence among individuals with more severe forms of CP, where poor gross motor function can be associated with decreased head control and dysphagia.[1] Individuals may experience anterior drooling, posterior drooling, or both. Anterior drooling, which manifests as saliva spilling out of the front of the mouth, can have significant psychosocial implications and may affect health related quality of life.[2] Posterior drooling is often not visible but can be associated with pooling of saliva in the posterior oropharynx leading to serious medical consequences such as chronic aspiration, recurrent respiratory infections and progressive lung disease. Respiratory related illness is a leading cause of death in children with CP, thus any interventions that lower the risk of pulmonary deterioration are important to consider.[3]

Prior to determining a treatment decision, clinical evaluation of the child with sialorrhea should be conducted via a multidisciplinary approach, either in real time or in series, with good communication between members of the child's health care team. Intervention should only be considered after all conditions that exacerbate drooling have been optimized, including oral health, trunk and head positioning, lip occlusion, airway obstruction, drug effects, allergy, gastroesophageal reflux and excessive mouthing. Figure 1, extracted from the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) Sialorrhea Care Pathway algorithm, outlines the important assessment steps as well as the objective and subjective assessment tools used for evaluating the extent and frequency of drooling and the impact it has on the child and family.[4]

Multiple interventions aimed at reducing or eliminating drooling have been described, however, there is no clear consensus on which are most effective. In 2012, a systematic Cochrane review analysed randomized and controlled clinical trials of drooling in individuals with cerebral palsy.[5] This helped to inform the Sialorrhea Care Pathway supported through the AACPDM.[4] However, there are a number of interventions that are used clinically in sialorrhea management for which there is limited or low level evidence about effectiveness and side effects. Due to Cochrane criteria, these were not included in their review. This paper outlines the full spectrum of interventions that have been reported for children with CP, including all levels of evidence, in order to inform the practicing clinician of the options available and the robustness of the literature behind those interventions.

Methods

A computer assisted literature search for relevant articles published from January 1978 to December 2018 was performed in PubMed with an additional manual search. The keywords and Mesh terms used in the search were "sialorrhea", "drooling", "hypersalivation",

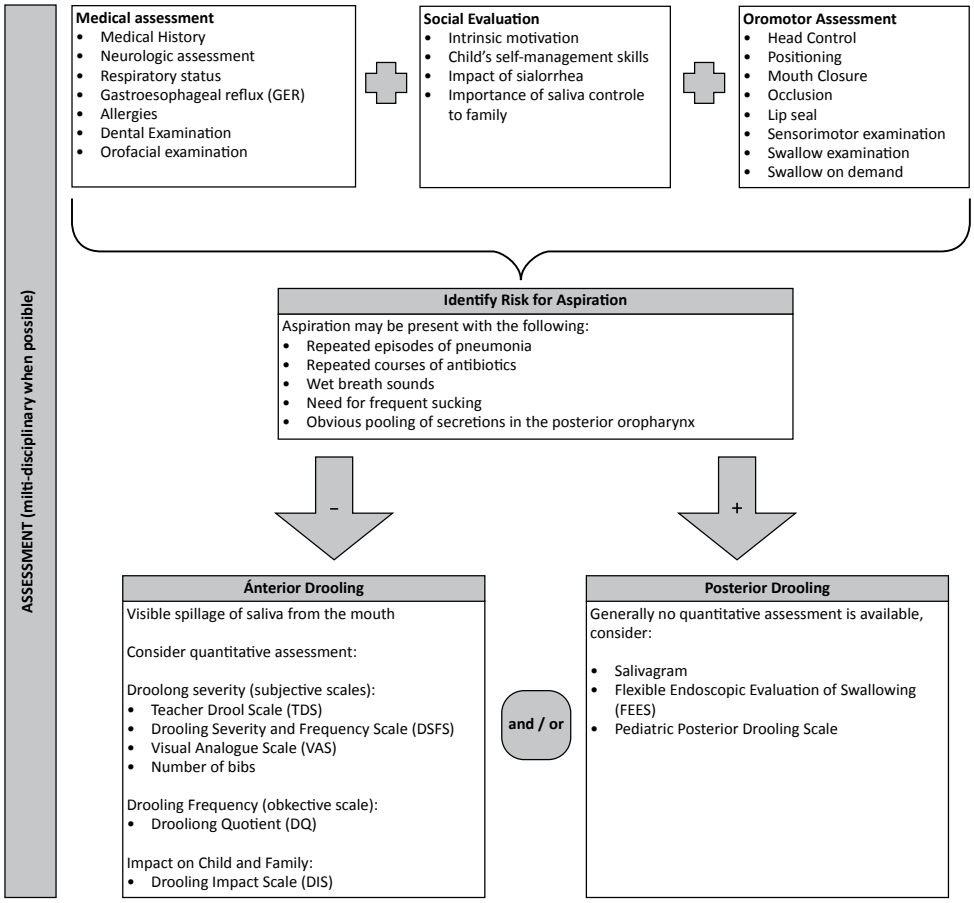

Figure 1. Flow Diagram for Evidence-informed Clinical Practice guideline for assessment of sialorrhea in Children/Youth with CP with subjective scales (the Teacher Drooling Scale (TDS)[41], the Drooling Severity and Frequency Scale (DSFS)[42], the Visual Analogue Scale (VAS)[43], and the Drooling Impact Scale (Drl scale)[18]); and the Drooling Quotient (DQ)[44] as an objective scale. The Pediatric Posterior Drooling Scale[45] is piloted as a new screening tool for posterior drooling.

"saliva loss" in various combination with "cerebral palsy", "spastic diplegia" and "spastic quadriplegia". Intentionally, no outcome was defined in the search strategy to prevent limitations in the search results. Inclusion criteria for the articles were English-language studies and those including individuals aged birth to 25 years. Initially the search was limited to studies including only participants with CP, however, in an effort to represent the full spectrum or clinically available interventions, the search strategy was broadened to include "neurodevelopmental disorders", "developmental disabilities", "motor skills disorders" or "intellectual disability". The methodological quality of each study was evaluated independently by two readers according to the American Academy of Neurology (AAN) Clinical Practice Guideline Process Manual, which defines four hierarchical classes of

therapeutic evidence (Table 1).[6] Consensus for grading discrepancies was achieved through discussion.

Table 1: American Academy of Neurology Clinical Practice Guidelines 6 (appendix II).

CLASSES	CRITERIA	RECOMMENDATIONS	CRITERIA
Class I	- Randomized controlled clinical trial or crossover trial in a representative population - Triple masked studies • period and carryover effects • statistical adjustments AND addition criteria a-e (see appendix II AAN)	High confidence (highly likely)	Requires at least two consistent class I studies
Class II	- RCT that lacks one or two Class I criteria a-e - Cohort studies employing methods that successfully match treatment groups on relevant baseline characteristics - Randomized crossover trial missing one of the following two criteria: a. Period and carryover effects described b. Baseline characteristics of treatment order groups presented - All relevant baseline characteristics are presented and substantially equivalent across treatment groups, or there is appropriate statistical adjustment for differences - Masked and objective outcome assessment*	Moderate confidence (likely)	Requires at least one class I study OR At least two consistent class II studies
Class III	- Controlled studies - Crossover trial missing both of the following two criteria: a. Period and carryover effects b. Presentation of baseline characteristics - A description of major confounding differences between treatment groups that could affect outcome - Outcome assessment performed by someone who is not a member of the treatment team	Low confidence (possibly)	Required at least one class II study OR At least two consistent class III studies
Class IV	Studies not meeting criteria for Class I-III	Very low confidence (insufficient)	When studies did not meet class I to III requirements OR Included studies that were conflicting

* Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation.

The full range of interventions for sialorrhea in individuals with CP is reported, with discussion of the level of evidence supporting each. This includes oral motor interventions, behavioral intervention, oral appliances, pharmacologic interventions, chemodenervation with botulinum toxin, and surgical options. The evidence is then considered in relationship to the treatment of children and young people with CP. Evidence not restricted to a diagnosis of CP is noted.

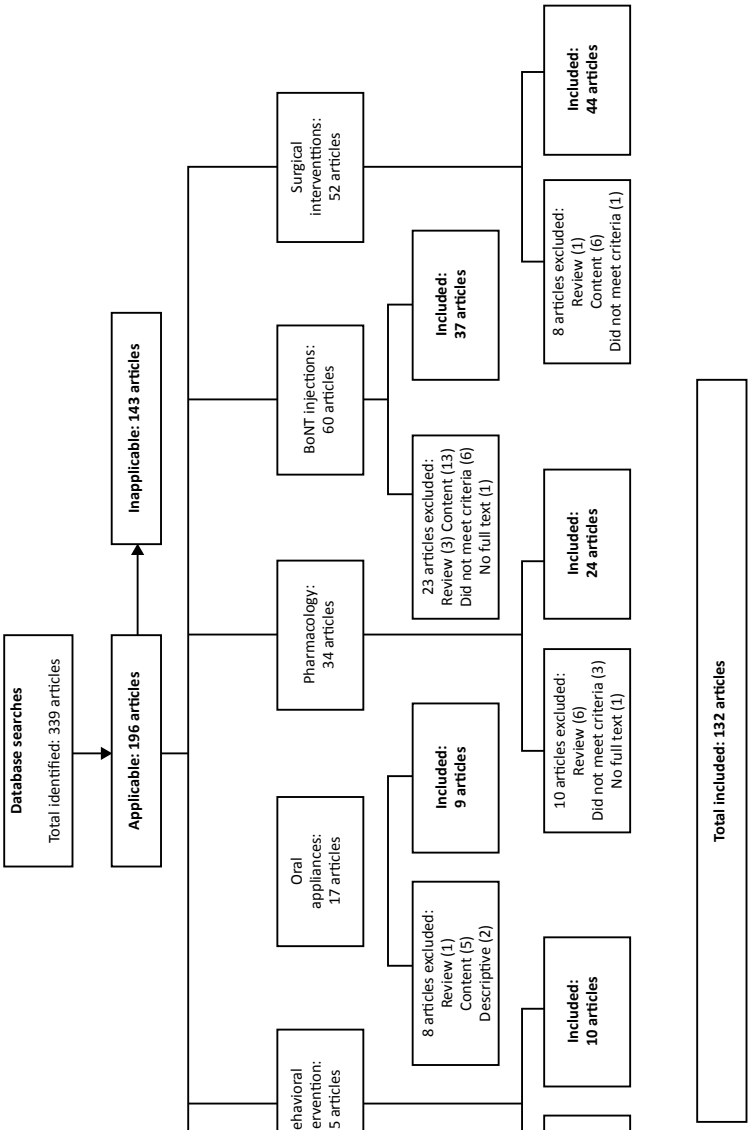

Figure 2. Literature Search Results.

RESULTS

A total of 339 articles were identified (figure 2) and 132 articles met criteria for inclusion. The following section outlines available treatment options, depicted in figure 3, for both anterior and posterior drooling in the context of the published literature supporting the use of each intervention.

Treatment of anterior drooling

Oral motor intervention

Oral (sensory) motor therapy may be used as a first step in treating anterior drooling. The aim of oral motor therapy is: (1) to reduce the anterior loss of saliva; (2) to increase oral awareness and swallow frequency; (3) to improve lip and jaw closure; (4) to increase tongue control, reduce tongue thrust; and (5) to improve oromotor tone and facial and oral sensation.[5] In general there are three main categories of oral-motor exercises (OME): active exercises, passive exercises, and sensory applications.[3]

Searches revealed 18 studies on the effects of oral motor interventions on drooling in mixed populations of children with neurodisabilities, including, but not restricted to, CP. One was excluded because it was a review, eight were excluded based on content and one was not available in full text. The remaining eight studies were classified as Class IV because of the lack of objective or masked outcome measures. In general, oral motor training for drooling had positive results. However, in Inal et al.'s randomized controlled trial the severity of drooling decreased after home based chewing training in the experimental group, but drooling frequency did not.[7] High level evidence supporting oral motor intervention is limited.

Behavioral Intervention

Behavioral interventions are aimed at changing the frequency or type of a target behavior. Antecedents (behaviors or events that precede the target behavior) and consequents (behaviors or events that follow it) are systematically manipulated or controlled to alter the target behavior. In young people with anterior drooling, the frequency of swallowing or wiping of the mouth and chin are examples of targets for behavioral intervention. Instructions, prompts and automatic cueing (e.g. beeps or vibrations from an electronic device or smart phone) are antecedent control techniques. Positive feedback, automatic reinforcement (e.g. music), and decelerative procedures (i.e. some kind of correction) are consequent techniques. These techniques are often used in combination. If changes in target behavior are achieved, withdrawal of the (external) support of therapists, parents and/or devices may result in increased drooling. Additional self-management techniques may help children with sufficient learning abilities to control target behaviors themselves and become independent from help and cues from their social or physical environment. Limited clinical

evidence from case-studies and two case-series on self-management techniques indicate that they may be an effective treatment for anterior drooling in this subgroup.[8, 9]

There is only low level evidence available for behavioral intervention for anterior drooling. Searches revealed 15 studies relevant to behavioral interventions. Two were excluded based on content and three were reviews. The remaining ten studies were all Class IV, mostly of single case experimental design, and included both children with CP and other neurodevelopmental disabilities. Based on references of three reviews from this search, an additional (manual) search for higher level evidence revealed no further studies. All 10 studies report improvement in drooling, but because of different dependent variables and/or modes of measurement it is not possible to comment on a consistent response rate. A recent systematic review by McInerney et al.[10] revealed low level evidence for the effectiveness of behavioral interventions to treat drooling, consistent with our findings but with slightly higher levels of evidence given a different grading metric.

Oral Appliances

Various oral appliances have been developed to modify and improve oral motor function and, in turn, saliva control. Use of the appliances is typically limited to children over six years of chronologic age. A multidisciplinary approach is essential as these appliances are prescribed by dentists, with input from speech pathologists and physicians needed to determine whether these are the correct approach, and to provide training, and monitoring. The most commonly described appliances are the palatal training appliance, the Castillo Morales appliance (CMA)[11, 12] and the Innsbruck Sensorimotor Activator and Regulator (ISMAR).[13] These appliances require daily use over an extended period. Compliance is a major limitation, both with palatal training devices[14] and with the ISMAR.[13] Oral appliances can pose risks during active seizures; individuals who use the ISMAR appliance must be able to breathe through their noses.

The literature search identified 17 articles possibly related to oral appliance use in young people with CP and related neurodevelopmental disabilities. Five articles were excluded due to unrelated content, two were descriptive and one was a review with a broader scope. Only nine met inclusion criteria, and all reflected Class IV evidence consisting of either anecdotal, single case studies or retrospective group studies without control groups. All these studies with small numbers of participants reported improvement in drooling, however, due to different methodologies, and outcome tools it is not possible to comment broadly on degree of improvement.

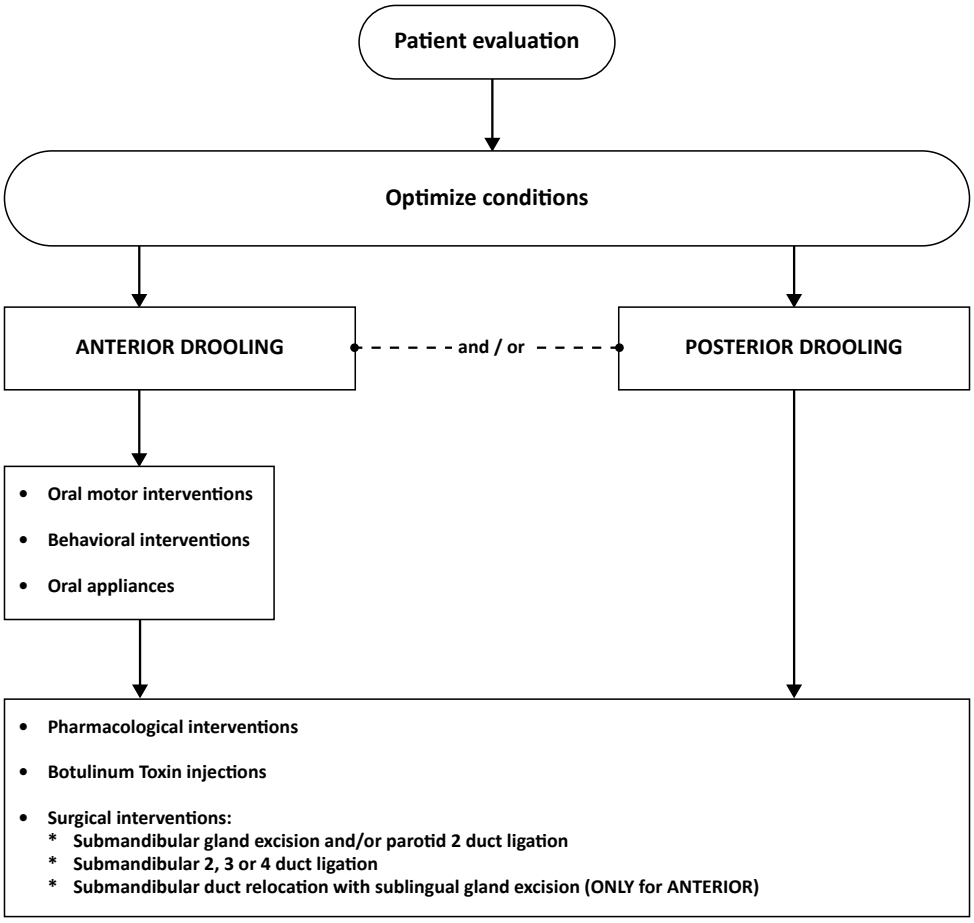

Figure 3. Interventions for sialorrhea from least to most invasive.

Treatment of anterior and posterior drooling

Pharmacologic Interventions

Anticholinergic pharmacological interventions are commonly prescribed for sialorrhea. These medications work by inhibiting stimulation of the salivary glands, thereby reducing the volume of saliva produced. The literature review revealed glycopyrrolate (glycopyrronium), scopolamine (hyoscine hydrobromide/scopolamine hydrobromide), benztropine, atropine, and trihexyphenidyl (benzhexol) to be studied in sialorrhea management in individuals with CP. Thirty-four articles were identified, ten of which were excluded because they either did not meet inclusion criteria (*n*=3), were reviews (*n*=6) or full text was unavailable (*n*=1). There were six Class III studies, two of which related predominantly to children with CP; the remainder included children with CP as well as a spectrum of neurodevelopmental

disabilities. Several studies supported the efficacy of glycopyrrolate and/or scopolamine. It should be noted that two of the studies would have been Class II except for the AAN requirement that objective outcome measures should be used. All other studies were Class IV (*n*=18), and most included children with both CP and other neurodevelopmental disorders.

Various systematic reviews and several randomized controlled trials studying the outcomes of pharmacologic intervention for drooling in children with CP and neurodevelopmental disorders have been completed.[5],[15] The effectiveness of glycopyrrolate,[21] scopolamine, [45] and benztropine[4] have independently been studied with RCTs and cohort studies of mixed evidence class, which have demonstrated drooling reduction in children and young people with CP. Side effects, however, are common and may include xerostomia, constipation, headache, thickened mucus, dehydration, urinary retention, urinary tract infections, fever, dizziness, drowsiness, skin rash, dilated pupils, blurred vision, and epilepsy.[3]

One of the strongest studies was the single blind randomized controlled drooling reduction intervention trial[16] comparing the effectiveness and side effect profile of scopolamine patches with orally administered glycopyrrolate in 90 children with CP and other neurodevelopmental disabilities. Findings suggested that both medications were equally effective in reducing drooling; however, glycopyrrolate was better tolerated by young people and parents. Following 12 weeks of treatment, 82% of those randomized to glycopyrrolate continued its use, compared to just 55% of those randomized to scoplamine. While scoplamine had fewer sides effects overall, when they occurred they were more likely to lead to treatment cessation. Unacceptable skin reactions to the patches were common and non-predictable side effects such as hyperactivity were seen.[17] As a result of these findings, the study authors recommended glycopyrrolate as the first line anticholinergic medication; however, the authors note that for some young people and parents scoplamine is well tolerated and convenient. There is not long-term safety data for either medication.

Sublingual atropine, trihexyphenidyl and inhaled ipratropium are three additional anticholinergic medications that are used clinically in some settings for drooling treatment. Our literature search did not reveal any studies of ipratropium in individuals with CP or neurodevelopmental disorders of childhood. Literature supporting the use of sublingual atropine and trihexyphenidyl is limited, but does show both to have few short-term side effects and to be effective in some individuals. The Drooling Impact Scale (Drl Scale) is a simple 10 item tool to assess the impact of drooling on a child.[18] A report comparing DrI Scale results pre- and post-treatment with sublingual atropine in 25 children with CP found a statistically significant decrease in drooling.[19] Sublingual atropine was well tolerated with just 12% of participants reporting side effects (flushing and fever; irritability; flushing and irritability; flushing and angioedema).[19] One class IV chart review of 101 children with CP reviewed outcomes with trihexyphenidyl and found a reduction in sialorrhea.[20]

In conclusion, there is evidence that glycopyrrolate and scopolamine are effective pharmacologic interventions for drooling reduction in children and young people with CP

but due to the strict criteria of AAN guidelines regarding objective outcome measures it was necessary to downgrade study scoring. The tradeoff between effectiveness and side effects may dictate which medication is used long term. Studies on benztropine also suggest effectiveness in treating sialorrhea. There is low level evidence that trihexyphenidyl and sublingual atropine demonstrate efficacy.

Botulinum Toxin

Injections of botulinum toxin into the salivary glands have a local anticholinergic effect to decrease saliva production. Botulinum toxin is frequently administered under general anesthesia, with ultrasound guidance for identification of the salivary glands. The maximum effect is typically seen after 2-8 weeks; improvement lasts an average of four to six months.[21] Due to its temporary effect, repeated botulinum toxin injections are typically required.

The literature search identified 60 articles related to botulinum toxin use for sialorrhea management, with 37 articles meeting inclusion criteria for this review. While the majority of the articles were graded as Class IV, there were two Class II and two Class III articles. The majority of articles focused on patients with CP (> 65% of study population), however one article included a mixed sample with just 29% of individuals carrying a CP diagnosis.

Injections may be performed to the submandibular glands (SMG), parotid glands (PG), or to a combination of both the SMG and PG. A prospective cohort study from 2010 in 131 children undergoing botulinum toxin injections to the submandibular glands alone found an objective and subjective response rate of 50%, with improvement for a median of 22 weeks.[22] In a controlled clinical trial, Jongerius et al. compared a single-dose botulinum toxin injection to the SMG with scopolamine treatment.[21] Results showed a significant decrease in drooling, with greatest reductions achieved 2 to 8 weeks post-injection. The side effect profile of botulinum toxin was preferable to that of scopolamine with 82% of patients reporting side effects from scopolamine. Restlessness was the most common reason to discontinue the medication. Following botulinum toxin injections, only mild incidental side effects were reported (5.1% transient flu-like symptoms; 7.7% mild swallowing difficulty).19 The efficacy of PG injections alone is similar to that of SMG injections. Most retrospective reviews report a moderate or good response with PG injections alone, ranging from 53-55%.[23, 24] Results of combined PG/SMG gland injections were reviewed in a randomized controlled trial of 24 children. Following injections, caregivers reported a satisfactory response rate in approximately 68% of individuals.[25]

Botulinum toxin injections have an overall favorable safety profile, however adverse side effects can occur. A cohort study of 209 children reported transient adverse events related to oral motor function in 33% of patients, 80% of which were characterized as mild. Onset was most commonly within one week (78.3%) and typically resolved by four weeks (53.6%).[26] Oral motor side effects seemed to occur most commonly, while pain, hematoma,

infection, rash, dry mouth, or thickened saliva were seen with less frequency.[24,27] Patients receiving higher doses of botulinum toxin were at a greater risk of side effects.[27]

Surgical Management

Surgical interventions are considered in patients with profuse, consistent anterior drooling, patients with persistent sialorrhea despite conservative measurements, and patients with a high risk of morbidity associated with lower respiratory tract infections due to posterior drooling. All procedures require patients to be under general anesthesia. Goals of surgical management include 1) redirecting salivary flow through rerouting or 2) eliminating salivary flow through ligation of salivary ducts or elimination of salivary glands.

The literature review identified 52 articles on surgical management of sialorrhea; 44 articles met inclusion criteria. All articles were graded as Class IV evidence. The review included outcomes for patient with CP and other neurodisabilities. The most commonly cited procedures included duct ligation (2, 3, or 4 duct), bilateral submandibular gland excision with or without bilateral parotid duct ligation, and relocation of the submandibular duct (SMDR) with or without sublingual gland excision (SLGE). When considering surgical interventions, providers must rule-out aspiration in patients prior to SMDR due to the risk of redirecting saliva to the base of tongue in a patient with a dysfunctional swallow.

Outcomes following SMDR demonstrate a significant reduction in sialorrhea.[28-30] Kok et al. also demonstrated a decrease in daily cares and economic consequences and an increase in socialization.[31] A comparison of outcomes of botulinum toxin and SMDR showed larger decrease in visual analogue scale (VAS) scores (a measure of subjective drooling severity over 2 weeks[31]) following SMDR than botulinum toxin injections, with 87.5% of patients reporting a statistically significant reduction.[32] SLGE is frequently performed with SMDR to prevent the complication of a ranula (blocked sublingual gland). The literature has shown that this decreases complications, but does not improve drooling outcomes.[33]

Bilateral submandibular gland excision may be performed in isolation or with parotid duct ligation. Performed in isolation, Delsing et al. reported an overall response rate of 63%, defined as a 50% reduction in drooling quotient (DQ: measures mean number of new drooling episodes every 15 seconds over 5 or 10 minutes).[34] This improvement persisted to 32 weeks. Noonan et al.[35] and Dundas and Peterson[36] reviewed outcomes following bilateral SMGE with parotid duct ligation. The response rate in their respective groups was favorable with Noonan et al tracking significantly fewer lower respiratory tract infections and Dundas and Peterson reporting a good to excellent response in 85% of individuals. Two retrospective reviews reported outcomes following duct ligations have been variable, ranging from 50% to 80% improvement.[37, 38]

Complications following all surgical interventions are varied, but include sialadenitis (salivary gland inflammation) following duct ligation, lingual nerve injury with SMD rerouting +/- SLG excision, and lingual nerve injury or marginal mandibular nerve injury following SMGE.

DISCUSSION

In our review of sialorrhea management for individuals with CP, as in the previous Cochrane review, there was a paucity of randomized and controlled clinical trials. In an effort to address clinician interest as well as geographic variability regarding choice and access to various treatment options, we have presented the full range of interventions for sialorrhea with the evidence base for effectiveness and associated side effects. Based on the results of this literature review, there is inadequate research to determine the effectiveness of oral motor therapy, behavioral therapy, oral appliances, and surgical interventions for sialorrhea management. The highest levels of evidence supported use of pharmacologic interventions, specifically glycopyrrolate, scopolamine and benztropine, and botulinum toxin injections into the salivary glands. Due to the strict criteria of the AAN guidelines, specifically the requirement for objective outcome measures, the grading for the interventions was largely limited to Class III and Class IV studies. The majority of the assessment tools used to measure drooling severity are subjective, which required downgrading of the research studies along these criteria. However, it is important to identify that perfectly objective criteria may never be possible to achieve in the context of sialorrhea outcomes. Meaningful outcomes may instead be measured by perceived quantity of drooling, ease of care, and quality of life outcomes which are captured with existing tools.[39] If this caveat is accepted, then the evidence supporting certain interventions is indeed upgraded, as noted below.

The literature on oral motor therapy is lacking with no agreement on effectiveness. The low level evidence and clinical experience of the speech and language therapist, however, suggest that active, functional and potentially passive exercises and sensory applications may be safely implemented in children with mild to moderate oral dysfunction, good cognitive skills, and who are highly motivated to address their drooling.[40] There is low level evidence regarding the efficacy of behavioral interventions and some indication that the use of behavioral techniques tailored to the individual's learning potential may help to reduce drooling in certain subpopulations. Similarly, there is low level evidence indicating positive impact of oral appliances on drooling.

Literature discussing surgical management of sialorrhea is limited by patient heterogeneity, small samples sizes, and the Class IV evidence. Regardless, it is our clinical expert opinion that when other interventions have failed and the expectation exists that children are not able to learn more oral motor control, surgical procedures for drooling management should be considered. There is regional variation with respect to the earliest age at which surgery is offered. None of the evidence supports a specific age range, however clinicians need to consider risks from general anesthesia as well as individual risk factors, such as the presence of aspiration and chronic lung disease at a young age. Specifically SMDR has shown improved outcomes over botulinum toxin injections, however the risk of aspiration following duct relocation requires consideration.[32] Based on the variability in

patient outcomes, 2, 3, and 4 duct ligation in isolation is typically not offered as the first line surgical intervention.

Recommendations for oral motor intervention, behavioral interventions, oral appliances, and surgical interventions are based on clinical expert opinion, rather than clinical research evidence. This was likely impacted by the stringent AAN guidelines mentioned previously. Surgical interventions appear to have great promise and the emerging literature indicates likelihood of efficacy. However, high quality research and objective outcome measures are needed to evaluate effectiveness and side effects of these approaches, the limitations for children with intellectual disability, and contraindications for children with certain diagnoses.

The highest levels of evidence were for several pharmacologic interventions and botulinum toxin injections. Based on the Drooling Reduction Intervention trial, glycopyrrolate is recommended prior to scopolamine as the first line pharmacologic agent for sialorrhea. Both drugs had documented effectiveness in reducing drooling; however, side effects from scopolamine were more likely to lead to treatment cessation. Nonetheless, the authors note scopolamine remains well tolerated and convenient for some young people and families. Benztropine is also probably effective. Trihexyphenidyl and sublingual atropine have encouraging low level evidence supporting their use in the treatment of sialorrhea in individuals with CP but further research is required.

Based on the literature review and expert opinion, botulinum toxin injections for sialorrhea management are considered to be likely effective. Limitations of the injections include the need for general anesthesia and their temporary effect, with a median improvement for 22 weeks.[22] Because of the risks of transient post-operative dysphagia, it is recommended that providers understand a patient's swallowing function prior to botulinum toxin injections.

There are a range of treatment options for sialorrhea management, with definitive recommendations limited by a lack of high-level evidence. This review does not delineate a specific order of interventions, but highlights the full range of treatment options as well as the published evidence for each intervention. A strength of this review is the international team of authors which provided information about the geographic trends and biases in treating sialorrhea. Additionally, discrepancies in grading of the articles by two independent reviewers were addressed via discussion and the use of a third unbiased reviewer. Limitations of the review include the limited research evidence; this meant it was not possible to create a clear step-wise path for treatment based on effectiveness data. There was a lack of long-term safety data and safety in treating very young patients with all interventions. More evidence to address these points is required for all interventions. Lastly, articles with a mixed sample of individuals with multiple diagnoses were included, with the results extrapolated to individuals with CP in areas we have highlighted. An international consensus defining best practices to evaluate treatment outcomes in sialorrhea management trials would be

helpful moving forward as we continue to determine which interventions are most valuable in treating sialorrhea in young people with cerebral palsy.

Disclosures

The authors wish to report that they created the Sialorrhea Care Pathway hosted by the American Academy of Cerebral Palsy and Developmental Medicine.

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CHAPTER 7

Diagnosis and management of drooling in children with progressive dystonia: a case series of patients with MEGDEL syndrome

D. Blommaert*
K. van Hulst*
F.J.A. van den Hoogen
C.E. Erasmus*
S.B. Wortmann*

* DB, KvH, CE, SBW contributed equally to this article

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Abstract

Drooling is a common problem in children with progressive dystonia. The authors noted a 58% incidence of drooling in 22/38 children with MEGDEL, a rare neurodegenerative cause of dystonia and report on the clinical course of four patients. Drooling of varying severity and subsequent respiratory problems were treated at the authors' multidisciplinary saliva-control outpatient clinic. One patient improved on antireflux medication, the second after medication with drooling as side effect was changed. Two other patients underwent salivary gland surgery, one of whom significantly improved; the other died shortly after surgery. The heterogeneity of the cases presented shows the need for stepwise and personalized treatment. The authors recommend the following: (1) optimize the treatment of the underlying neurological condition and replace medication that stimulates saliva secretion; (2) treat constipation, scoliosis, and gastroesophageal reflux if there is still a risk of chronic aspiration of saliva; (3) perform more intense/invasive treatment (botulinum toxin, salivary gland surgery).

Dystonia is a movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. It is classified on the basis of its clinical characteristics (age at onset, body distribution, temporal pattern, and associated features) and etiology, which includes nervous system pathology and inheritance.[1] MEGDEL syndrome (MIM # 614739, *SERAC1*) has recently been described as a new deafness-dystonia syndrome and the number of affected patients is rapidly increasing (the author's database has 60 patients).[2,3] MEGDEL syndrome is characterized by 3-*ME*thyl*G*lutaconic aciduria, dystonia, *D*eafness, *E*ncephalopathy, and neuroradiological features of *L*eigh-like disease. The dystonia becomes apparent in infancy, is multifocal or generalized progressive, and persistent, and is accompanied by other neurological features such as axial hypotonia and progressive limb spasticity.

Children with neurological disorders often experience swallowing and feeding problems, which can lead to excessive pooling of saliva in the anterior oral cavity, resulting in drooling.[4] Drooling can be divided into anterior drooling and posterior drooling.[5] Anterior drooling is the unintentional loss of saliva from the lips, which leads to perioral infections, rejection by peers, and, when excessive, dehydration and damage of electronic devices in daily life. Posterior drooling refers to the spilling and pooling of saliva posteriorly into the oropharynx and hypopharynx. In children with severe pharyngeal dysphagia, the chronic aspiration of saliva can lead to cough, choking incidents, recurrent lower airway infections, or lung injury.[5-7] Intestinal dysmotility is also common in children with neurological disorders and is caused by dysfunction of the brain-gut axis that controls the function of the entire gut, via the vagal nerve. Disturbances of the axis lead to gut motility disorders, gastroesophageal reflux disease, and constipation.[5,8,9] The mechanisms by which these disorders give rise to drooling are not completely understood, but it is known that constipation aggravates gastroesophageal reflux disease, and that gastroesophageal reflux disease can increase sialorrhea via the esophago-salivary reflex.[10-12] Therefore, treatment of gastroesophageal reflux disease and constipation may indirectly have a positive effect on drooling.

Little is known about the treatment of drooling in children with progressive dystonia. On the basis of a case series of 4 patients with MEGDEL syndrome, the authors propose a stepwise approach to the treatment and aftercare of drooling in children with progressive dystonia.

Methods

The author's (SBW) database consists of 60 patients with genetically proven MEGDEL syndrome, four of whom are being treated at the Multidisciplinary Saliva-Control Outpatient Clinic, Radboudumc, Nijmegen, the Netherlands. A questionnaire about the clinical course, including questions about drooling, was sent to the physicians caring

for the other 56 patients. The data about the clinical course will be published in a separate article.

A multidisciplinary specialist team consisting of a pediatric neurologist, otorhinolaryngologist, rehabilitation physician, and speech language therapist assessed the patients. The assessment took 2 to 3 hours. It started with review of the patient's medical and socialemotional history, including evaluation of the patient's (or carer's) motivation and ability to participate in possible treatment. Special attention was paid to oral hygiene, eating and drinking habits and abilities, nutritional state, the presence of allergies, as well as signs and symptoms suggestive of gastroesophageal reflux disease, constipation, or respiratory and neurological problems.[5,13]

The physical and neurological examinations focused on positioning, muscle tone, and movement disorder; ear, nose, and throat condition; dental status; oral functions; and speech and swallowing skills. The combined Drooling Severity and Frequency Scale was used to assess the quality and quantity of drooling.[14] The severity of drooling was scored from 1 to 5 (1 = dry, never drools; 2 = mild, wet lips; 3 = moderate, wet lips and chin; 4 = severe, damp clothes; 5 = profuse, wet hands/clothes/objects) and the frequency of drooling was scored from 1 to 4 (1 = never, 2 = occasionally, 3 = frequently, 4 = constantly drools). Depending on the assessment outcome and patient characteristics (age, diagnosis, cause of drooling, and the safety of swallowing), the team drew up a multistage proposal for treatment (speech and language therapy, physical therapy, behavioral, pharmacological, and surgical therapy) and communicated this to the patient and his or her carers. Follow-up measurements were standardized after treatment (outpatient clinic visit or telephone consulting).

Results

Data on drooling were available for 44 of the 60 patients in the authors' database. Drooling was reported in 22 patients, giving an incidence of drooling in MEGDEL syndrome of 58% (22/38).

All four patients with genetically proven MEGDEL syndrome treated at Radboud UMC showed a characteristic clinical course. Their development was normal or delayed until about 2 years of age, when there was rapid deterioration with progressive bilateral spasticity and dystonia. All patients exhibited hearing loss, severe intellectual disability, and lack (or loss) of speech development. All were wheelchair bound. Feeding problems led to failure to thrive and necessitated gastrostomy tube feeding; all four patients had gastroesophageal reflux disease. The disorder was slowly progressive and all four patients developed progressive drooling for which they were referred to the Multidisciplinary Saliva-Control Outpatient Clinic. The findings are summarized in Table 1.

Patient A, a girl, was first evaluated when she was 15 years old (155 cm tall [P2-16]; weight 35 kg [P2]). She had severe encephalopathy with persistent, generalized dystonia.

Her parents said that she had thick, mucous sputum and that she daily had several attacks of coughing, retching, choking, and dyspnea. The frequency of attacks had increased with time and attacks were worse at night. She suffered from recurrent pneumonia. She was being treated with omeprazole, polyethylene glycol, baclofen, and prophylactic co-trimoxazole.

On examination, severe and frequent anterior drooling was noted, together with intermittent torticollis (based on a pathological asymmetric tonic neck reflex combined with dystonia) with a strong tonic bite reflex, which caused her to bite her cheeks and lips. She tended to gurgle and choked on her saliva; her cough was insufficient to clear the larynx. Bilateral submandibular gland excision and bilateral parotid duct ligation were performed, without complications, to reduce the amount of saliva produced. Six months after surgery, her drooling had improved substantially—the severity of anterior drooling had decreased from severe (Drooling Severity and Frequency Scale score 4) to dry (Drooling Severity and Frequency Scale score 1) and its frequency diminished from frequently (Drooling Severity and Frequency Scale score 3) to never (Drooling Severity and Frequency Scale score 1). The patient had gained 8 kg (P50, weight for height) and no longer had recurrent airway infections (she was still taking antibiotics). She is now 19 years old and her condition is stable with no recurrence of drooling (Drooling Severity and Frequency Scale score 1 for severity and 1 for frequency).

Patient B, a girl, visited the Multidisciplinary Saliva-Control Outpatient Clinic when she was 15 years old. She suffered from continuous anterior drooling and posterior drooling with gurgling and sporadic episodes of aspiration and vomiting without efficient cough. The latter had become more frequent in the last few weeks. Her parents tried to remove mucus, using mechanical tracheal suctioning, several times a day but her brisk tonic bite reflex and trismus made this virtually impossible. Her parents reported that at night she breathed irregularly with long periods of apnea. She had been treated for recurrent aspiration pneumonia several times in the last few years and had severe restrictive lung disease. Despite treatment with omeprazole, polyethylene glycol, baclofen, pipamperone, melatonin, and prophylactic co-trimoxazole, her respiratory condition was deteriorating rapidly.

On physical examination, the patient exhibited spasticity of the arms, dystonia of the fingers, and no functional motor control of the lower extremities. She experienced less trouble when she sat in a supported sitting position than when she was lying down. Bilateral submandibular gland excision and bilateral parotid duct ligation was performed without complications, to improve her pulmonary condition; however, her respiratory status and overall condition continued to deteriorate and she was ventilator dependent. Treatment was stopped on the third postoperative day and the patient died immediately thereafter.

Patient C, a girl, was seen when she was 21 months old. She suffered from severe agitation, insomnia, spasticity of the extremities, and continuous tongue protrusion; the latter had become progressive in the last few months and was worse when she was tired, resulting in increased saliva production. This caused attacks of anxiety, choking, and

Table 1: Oral Motor Findings of Patients A, B, C, and D Before and After Treatment.

	A	B	C	D
Feeding				
Oral feeding/tube feeding	–/+	–/+	–/+	–/+
Gastroesophageal reflux				
Reflux disease/medication	+/+	+/+	+/+	+/-
Constipation	+	+	-	+
Respiratory status				
Gurgly voice	+	+	+/-	+/-
Weak cough	+	+	+	-
Dyspnea/chronic cyanosis	+	+	+	-
Obstructive respiratory problems	+	+	+	-
Recurrent lower airway infections or pneumonia	+	+	+	+
Prophylactic antibiotics	+	+	+	-
Oral motor skills				
Voluntary movements	-	-	-	+/-
Pathological oral reflexes (tonic bite, gagging)	+	+	+	+
Hyperkinetic oral movements	-	+	+	-
Trismus	-	+	-	-
Tongue protrusion	-	-	++	+
Oral swallow phase				
Disturbed	+	+	+/-	+/-
Pharyngeal swallow phase				
Delayed initiation	+	+	+	+/-
Residue after swallow	+	+	-	-
Saliva pooling	+	+	+/-	+/-
Choking	+	+	+/-	+/-
Aspiration	+	+	+/-	+/-
Drooling				
Anterior	+	+	++	+/-
Posterior	++	++	+	+/-
Anterior drooling severity scale baseline[a]	4	N/A	3-4	4-5
Anterior drooling frequency scale baseline[a]	3	N/A	4	4
Intervention	Bilateral submandibular gland excision and parotid duct ligation	Bilateral submandibular gland excision and parotid duct ligation	Advice to interrupt tongue protrusion, adenotonsillectomy	Feeding advice, antireflux medication
Anterior drooling severity after treatment[a]	1 (8 m) 1 (4 y)	N/A N/A	N/A N/A	3 (8 m) 4/5 (1 y)
Anterior drooling frequency after treatment[a]	1 (8 m) 1 (4 y)	N/A N/A	N/A N/A	3 (8 m) 4 (1 y)

M, months; y, years; –, absent; +, present; +/–, occasionally present; ++, evident; N/A, not applicable.
[a]Drooling Severity and Frequency Scale.[14]

dyspnea and exacerbated her agitation. Her cough was weak and she recently had aspiration pneumonia twice. The development of frequent partial complex seizures made it almost impossible for her parents to care for her (e.g. changing clothes). She was being treated with ranitidine, polyethylene glycol, ondansetron, levetiracetam, diazepam, risperidone, levomepromazine, and prophylactic co-trimoxazole.

On physical examination, the infant was found to have encephalopathy with truncal hypotonia, frequent dystonic movements, ataxia, and myoclonus made independent sitting impossible. She showed mild anterior drooling. When the authors tried to initiate swallowing by placing a droplet of water on her tongue, it took her some time to interrupt the tongue protrusion to swallow. During swallowing, the droplet was moved dorsally and weak swallowing was heard upon cervical auscultation. The continuous tongue protrusion

led to increased saliva production and prevented the initiation of swallowing. Her parents were shown how to interrupt the tongue protrusion by stabilizing the jaw, to trigger a swallow and prevent pooling of saliva in the mouth. It was suggested that risperidone and levomepromazine should be tapered off (to reduce potential extrapyramidal side effects) and trihexiphenidyl should be started (to improve dystonia and use anticholinergic side effects). However, the parents were unable to accept any treatment suggestions. Adenotonsillectomy was performed elsewhere, which had a modest effect on the frequency of infections and the general quality of life (evaluated by the referring physician and the parents). Unfortunately, the parents refused further follow-up or treatment.

Patient D, a girl, was seen when she was 4 years old. Oral feeding was supplemented by tube feeding. Her parents reported tongue thrusting and gagging during eating and that she sometimes aspirated and then coughed. The child had developed aspiration pneumonia once after vomiting during gastroscopy. Several times a year she was admitted to the local hospital for infections of the airway, and she regularly vomited her food and thick sputum. She was being treated with baclofen, polyethylene glycol, alimemazine, erythromycin, and ibuprofen.

On physical examination, dystonia with ‘‘sensory tricks’’ (right fist under chin, a ‘‘geste antagoniste’’ which may serve to temporary interrupt dystonia symptoms) and severe tongue protrusion were evident. Pathological biting and gagging reflexes were present, and her mouth was constantly wide open. Minimal oral voluntary movements were possible. Anterior drooling was continuous and was profuse during activities, depending on her posture. Her pharyngeal swallow function seemed sufficient and there was no residue after feeding; however, some saliva pooling (posterior drooling) was observed at rest.

Antireflux medication was started and her parents were advised to feed her with her positioned with an extended neck and not to give oral feeding when she was tired. No further respiratory infections occurred during the 6-month follow-up and the drooling improved. However, the drooling subsequently worsened and the child experienced severe choking and vomiting. Because of the deterioration in the girl’s overall condition, her parents were reluctant to let her undergo narcosis for invasive antidrooling treatment and also refused anticholinergic medicines to reduce the drooling because of their potential side effects.

Discussion

These patients with MEGDEL syndrome illustrate the different aspects of diagnosing and treating anterior drooling/posterior drooling in children with progressive dystonia. The authors are well aware that this study has some limitations. The sample size is small and MEGDEL syndrome is a rare disorder. However, it allows us to illustrate the heterogeneity in severity of drooling, interventions performed and outcome in a group of patients with a homogenous course of disease. Although all four children had anterior drooling, neither

the parents nor the Multidisciplinary Saliva-Control Outpatient Clinic team considered it the main problem, possibly because the children had severe intellectual and physical disabilities and lack or loss of speech, problems that already severely limited the children socially in daily life, making anterior drooling less relevant. Posterior drooling is often more difficult to recognize and can lead to aspiration pneumonia, a life-threatening condition that was the reason for referral of the four children to the Multidisciplinary Saliva-Control Outpatient Clinic. Treatment should be personalized based on knowledge of the complex and interacting factors that influence saliva secretion and which involve the whole brain-gut axis (especially gastroesophageal reflux disease and constipation). Contributing factors should be evaluated and treated if necessary, starting with the least invasive intervention (figure 1).

In the authors' proposed management strategy, the first step is to optimize, in terms of minimizing drooling as a side effect, drug therapy for the underlying neurological disorder. In patients A, B, and D there was no need and/or possibility to alter their medication. In patient C, the authors advised that drugs that affect saliva secretion, such as neuroleptic drugs or benzodiazepines, should be tapered off or replaced by drugs with fewer side effects. However, the parents did not accept the authors' advice.

The second step is to improve supportive treatment for problems associated with the brain-gut axis, such as constipation, enteric dysmotility, and gastroesophageal reflux disease.[6,8,9] This intervention had satisfactory results in patients A to C. A proton pump inhibitor was started in patient D, which had a beneficial effect on drooling but was of limited duration (Table 1). The authors always advise parents about oral hygiene, and a speech-language therapist shows parents and carers how to feed the child safely (see patient D).[15] The child needs to be seated upright, which often necessitates use of a special chair or adapted corset.[8] It should be remembered that scoliosis may aggravate gastroesophageal reflux disease.[8] In general, children with complex neurological disorders often have many problems with swallowing, as seen in the authors' patients, and their general condition and ability to swallow may fluctuate, depending on a number of factors, such as fatigue, distraction, positioning, and so on. For this reason, the authors usually recommend giving food and fluid via a gastrostomy feeding tube, with supplementary food being given orally on ''good days.'' An otorhinolaryngologist should evaluate whether tonsillectomy could facilitate swallowing by reducing pain, obstruction, and recurrent infections.[16] The parents and doctor of patient D considered that tonsillectomy improved the situation, but unfortunately the parents refused further follow-up, and so the authors cannot comment on the indication and effect of this treatment.

If despite conservative measures posterior drooling persists, more aggressive treatment such as anticholinergic drugs, botulinum toxin type A injections, or surgery, is necessary (third step). A systematic review found some evidence that anticholinergic drugs are effective in the treatment of drooling in children with multiple handicaps.[15] However, the side effects of these drugs (psychiatric symptoms, constipation, urinary retention) should be taken into account, because they may exacerbate the symptoms of MEGDEL syndrome.

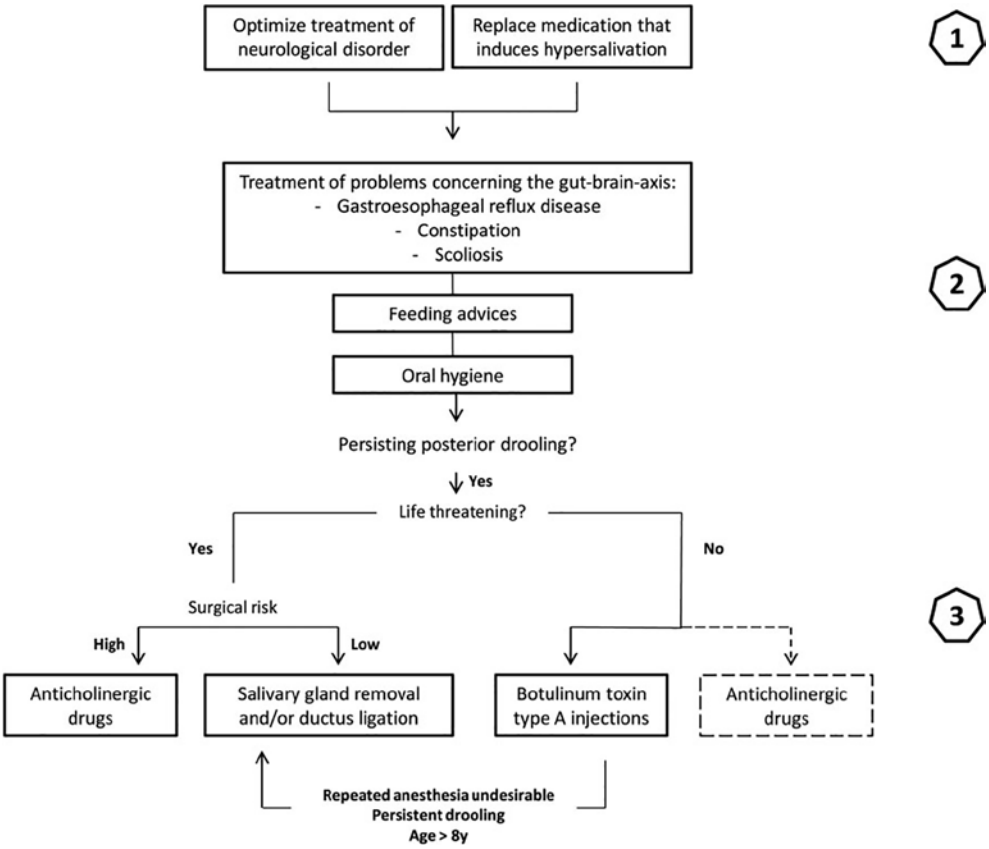

Figure 1. First, treatment of the neurological condition has to be optimized, if possible. Second, supportive treatment should be improved. Third, when a risk for chronic salivary aspiration remains, more invasive treatment follows.

Local ultrasound-guided injection of botulinum toxin type A into the submandibular and/or parotid salivary glands under anesthesia decreases drooling.[13] However, changes in the viscosity of saliva (saliva becomes thicker) can exacerbate swallowing problems as a side effect.[17] Existing swallowing problems are a strong predictor of increased swallowing problems after botulinum toxin type A (unpublished data), and therefore it is essential to investigate oral motor function before treatment. Because patients A, B, and C had weak oral motor control, the authors did not advise botulinum toxin type A injections. Patient D had sufficient oral motor function, making botulinum toxin type A injections a potential treatment option in the future. However, it should be realized that botulinum toxin type A is not a permanent therapy, which makes it less suitable for children with inherited and progressive neurological disorders such as MEGDEL syndrome.[4,17]

There are several surgical options to treat drooling with more long-lasting effects. One successful procedure is submandibular duct relocation. This approach is, however,

contraindicated in children with MEGDEL syndrome because the ducts are moved from the anterior oral cavity to the base of the tongue, so that saliva passes directly into the oropharynx. In children with a weak oral motor function, the procedure increases the pooling of saliva in the oropharynx and consequently increases the risk of posterior drooling and aspiration pneumonia.[18] Duct ligation is another surgical technique to improve drooling and has been found to reduce anterior drooling and possibly posterior drooling.[19] Both procedures require skilled ear, nose, and throat surgeons. Salivary gland removal, which is often performed during otorhinolaryngological procedures, results in a long-lasting decrease in drooling.[20,21] It is important to monitor dental health after a surgical procedure or botulinum toxin type A injections, because of an increased the risk of dental caries because of the reduced protective role of saliva.[22,23]

Currently, there is no evidence to support one surgical option over another. The authors opt for comprehensive surgery in children older than 10 years if their medical condition is life-threatening (due to severe chronic pulmonary aspiration) and the child's health is too weak for repeated anesthesia. Bilateral removal of the submandibular gland and bilateral ligation of the parotid duct improved the general clinical condition of patient A, although prophylactic antibiotics are still required, which is not uncommon in children with severe multiorgan disease even without drooling. Unfortunately, the respiratory status and overall condition of patient B were too fragile to wean her off ventilation after surgery and she subsequently died. This underlines the need for early referral to a specialized center to save lives.

In conclusion, drooling is a common serious problem in children with MEGDEL syndrome. Although this study was limited by the small number of patients included and the short follow up period of maximally 4 years, the authors suggest a stepwise with multidisciplinary aftercare to diminish drooling in these and other patients with progressive dystonia. Tailored recommendations can improve respiratory health and symptom-free survival.

Authors' Note

Authors DB, KVH, CEE, and SBW contributed equally to this article.

Ethical Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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8

CHAPTER 8

Negative effects of submandibular botulinum neurotoxin A injections on oral motor function in children with drooling due to central nervous system disorders

K. van Hulst
C.V. Kouwenberg
P.H. Jongerius
T. Feuth
F.J.A. van den Hoogen
A.C.H. Geurts
C.E. Erasmus

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Abstract

Aim: The aims of this study were: (1) to determine the incidence and nature of adverse effects on oral motor function after first injections of botulinum neurotoxin A (BoNT-A) in submandibular glands for excessive drooling in children with central nervous system disorders; and (2) to identify independent predictors of these adverse effects.

Method: A cohort study involved 209 children (123 males, 86 females, aged 4–27y, median 8y 4mo), who received submandibular BoNT-A injections for drooling. Adverse effects were categorized into swallowing, eating, drinking, articulation, and other problems. Univariable logistic regression was used to study differences in patients with and without adverse effects. Possible predictors were identified using multivariable logistic regression.

Results: Transient adverse effects occurred in 33% of the 209 BoNT-A treatments. Almost 80% of these were mild, versus 8.7% severe. Approximately 54% of the adverse effects spontaneously resolved within 4 weeks; 3% still existed after 32 weeks. A diagnosis of cerebral palsy, higher range of BoNT-A dosage, and a pre-treatment drooling quotient < 18% were found to be independent predictors of adverse effects.

Interpretation: Before using submandibular BoNT-A injections for drooling, potential adverse effects should be discussed. Oral motor function needs to be monitored, because existing dysphagia may be worsened. The identified clinical predictors could be helpful to optimize patient selection.

Treatment with botulinum neurotoxin (BoNT) in the salivary glands is a widely accepted effective intervention for drooling in children with central nervous system (CNS) disorders. When injected into the salivary glands, BoNT inhibits the acetylcholine release at the terminal nerve endings, decreasing the secretion of saliva and diminishes drooling in the majority of patients.[1]

The main group of children with neurological impairments treated with BoNT injections are children with cerebral palsy (CP), a vulnerable group with a spectrum of oral motor problems (estimated 40% drooling prevalence).[2-4] Drooling has a serious impact on the children's social interaction, self-esteem, and health.[5] The effectiveness of salivary gland BoNT has been studied extensively, although the debate about which glands should be injected is still going on. Several studies demonstrated that, after BoNT, drooling is significantly reduced. In Scheffer's study a clinically notable response was found in 46.6% of children.[6] The duration of this effect was approximately 2 to 6 months (median 22wks).[6-8] In most of these studies, botulinum neurotoxin A (BoNT-A) was used.[9]

Considering the increasing use of BoNT for drooling, studies to identify possible risk factors for adverse effects on oral motor functions before treatment are urgently needed.10 Post-intervention assessments showed that adverse effects on oral motor functions with a potential negative effect on swallowing occurred from 0%[11-13] up to 17.8%[6] of the cases after submandibular gland injections, and up to 33%[14] of the cases after combined submandibular/ parotid gland injections. To date no major complications were identified after submandibular injections.

Knowledge of the incidence, nature, and risk factors of adverse effects will help to predict which children with CNS disorders will positively qualify for BoNT to ameliorate excessive drooling.

The objectives of this study were: (1) to determine what adverse effects on oral motor function occur up to 8 months after the first BoNT-A injections in the submandibular glands; (2) to describe the incidence and course of these adverse effects; and (3) to identify independent predictors for adverse effects on oral motor function.

Method

Design and patient selection

In this cohort study, 209 children (123 males, 86 females; median age at inclusion 8y 4mo, aged 4–27y) participated. Inclusion criteria were: (1) first treatment with BoNT-A injections in the submandibular glands in the period between January 2002 and May 2013; (2) moderate to severe drooling with a score of three or higher on the Teacher Drooling Scale (occasional drooling, intermittent, all day); (3) minimum age of 4 years; (4) a minimum of two measurements representing baseline and at least one follow up; and (5) no previous surgical procedure for saliva control.

Informed consent for BoNT-A treatment was obtained from the child's legal representative(s). Parents or caregivers were informed about the consequences and the expectations of the treatment before the injections. All injections were administered as part of regular care.

Patient characteristics

All children were assessed before treatment by members of the multidisciplinary saliva control team of the Radboud university medical center. A medical assessment was performed by the pediatric neurologist and the ear, nose, and throat (ENT) specialist. Two specifically trained speech and language therapists (SLTs) carried out a social evaluation and an oromotor assessment. The quantity of drooling and the impact of the intervention on the severity of drooling were measured with objective and subjective scales at three different moments: before (t1), 8 weeks (t2), and 32 weeks after the injections (t3). The severity of drooling was quantified with the modified drooling quotient.[15] A caretaker visual analogue scale score (range 0–10) reflected the severity of drooling, with 0 indicating 'no drooling' and 10 indicating very severe drooling.[5] Based on direct SLT observations and parental reports, the viscosity of saliva was judged before and after BoNT-A (more serous/ more mucus/unchanged).

Treatment characteristics

Intraglandular injections of BoNT-A (Botox; Allergan, Nieuwegein, the Netherlands) were performed by the team's pediatric rehabilitation specialist under ultrasound guidance and general anesthesia. Treatment consisted of bilateral injections in the submandibular glands. Botox was diluted in saline 0.9% (25U/mL). Using a Spinocan needle, 1ml was divided over two or three sites throughout the gland. Occasionally, slightly more BoNT-A was injected to attain optimal spread, up to a maximum of 30U Botox per gland. For every child the applied dosage of BoNT-A per gland was noted in the medical records. The clinically relevant response at t2 to BoNT-A treatment was defined as ≥ 50% reduction in drooling quotient and/or a reduction of 2 standard deviations from the baseline visual analogue score to obtain a combined objective and subjective outcome.[6]

Adverse effects

If the caregivers noticed any post-treatment change in oral motor function during the first 8 weeks, they were encouraged to contact the SLT for advice and, if needed, they were invited for an additional visit at the outpatient clinic. Adverse effects were elicited as a part of our usual care during each follow up moment at 8 weeks and 32 weeks through a semi-structured interview. During the SLT measurements at t2 and t3, we specifically asked for any probable adverse effect or change in health condition. Negative oral motor problems were recorded and categorized according to the International Classification of Functioning, Disability and Heath, Children and Youth version (ICF-CY). Five subdomains remained: (1) saliva swallowing=reported changes in saliva viscosity, increased choking on saliva, and/

or reported discomfort during swallowing saliva; (2) eating=reported discomfort during eating (coughing, gagging), deteriorated feeding pattern; (3) drinking=reported discomfort during drinking (coughing, choking, dyspnoea); (4) articulation=reported deteriorated speech; (5) other problem=reported other discomfort, as sore throat, dry mouth/lips, and teeth grinding. Adverse effects were subdivided into three categories: mild, moderate, and severe (definitions in Table 2). The predefined outcome definition was dichotomous: adverse effects occurrence 'yes' versus 'no'.

Statistics

Descriptive statistics were used to determine general characteristics of the children and allocated treatments, and the incidence and occurrence of the adverse effects. Medians and minimal/maximal values were calculated for continuous variables. The association between post BoNT-A saliva viscosity (more concentrated mucus saliva) and the appearance of adverse effects was calculated by a chi-squared test, as well as the relationship between the occurrence of adverse effects and the response to BoNT-A injections. Univariable logistic regression was used to study associations between patient characteristics, the BoNT-A dosage, and the occurrence of adverse effects. The adverse effects prevalence (*n*) and the crude odds ratio (OR) with 95% confidence intervals (CI) are presented. Potential predictors of adverse effects incorporated in the model were based on biological plausibility and a previous publication of the drooling quotient.[15] Model selection was done using backward stepwise elimination with $p = 0.100$ levels of removal. Results with two-tailed p-values <0.050 were considered significant. The adjusted ORs with 95% CI of the final model were calculated. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was used as a measure of predictive discrimination. Missing descriptive values were considered as missing completely at random (MCAR). To calculate treatment responses, missing values of drooling quotient and visual analogue scores were imputed according to the worst-case scenario: missing data were replaced with the last previous observation or replaced by baseline values. Statistical analyses were carried out using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Patient and treatment characteristics

Our data set of 209 children contained 130 children with CP (62.2%), whereas 78 children (37.3%) were classified as non-CP (e.g. epileptic encephalopathy or neurogenetic syndromes) (Table 1). The disease course was complicated by intractable seizures in 18 children (8.6%). All children had received bilateral submandibular BoNT-A injections, 182 (87.1%) with a dosage of 25U, 16 (7.7%) had received <25U per gland, and 8 (3.8%) had received more than 25U per gland. Most children (*n*=136; 65%) were classified as responders, whereas 73 (35%) were considered to be non-responders at t2.

Table 1: Characteristics of study population at baseline (t1) (*n*=209).

Patient characteristics	*n* (%)
Sex	
Male	123 (58.9)
Female	86 (41.1)
Age at inclusion	
Median	8.4 (4.1–27.8)[a]
Diagnosis	
CP	130 (62.2)
Non-CP[b]	78 (37.3)
Unknown	1 (0.5)
Disease course[c]	
Complicated	18 (8.6)
Non-complicated	190 (90.9)
Unknown	1 (0.5)
Mental ability	
Developmental age <4y	131 (62.7)
Developmental age >4y	78 (37.3)
Degree of mobility	
Ambulant	104 (49.8)
Non-ambulant	105 (50.2)
Cause of drooling	
Low cognitive awareness	25 (12)
Impaired oral phase of swallowing	126 (60.2)
Impaired oropharyngeal phase of swallowing	58 (27.8)
Nutrition intake	
Tube/tube and oral	34 (16.3)
Oral	175 (83.7)
Choking on saliva	
Yes	59 (28.2)
No	145 (69.4)
Unknown	5 (2.4)
Choking on food	
Yes	96 (45.9)
No	109 (46.8)
Unknown	4 (1.9)
Choking on drinks	
Yes	107 (51.2)
No	99 (47.4)
Unknown	3 (1.4)
DQ	
Median	27.5 (0–100)[a]
Unknown	2 (1)
VAS	
Median	8 (3.4–10)
Unknown	2 (1)
Treatment characteristics:	
Dosage of BoNT-A per gland, *n* (%)	
Dosage<25U	16 (7.7)
Dosage=25U	182 (87.1)
Dosage>25U	8 (3.8)
Unknown	3 (1.4)
Saliva viscosity at t2, *n* (%)	
More serous	17 (8.1)
More mucus	76 (36.4)
Unchanged	76 (36.4)
Unknown	40 (19.1)
Treatment response,[d] *n* (%)	
Responder	136 (65.1)
Non-responder	73 (34.9)

[a] Data of age, DQ and VAS are presented as median (min/max).
[b] Non CP: children with developmental disability mainly as part of a syndrome, genetic, metabolic or neurodegenerative disorder.
[c] Complicated: in case of a progressive disease or if something unexpected happened (e.g. uncontrolled epilepsy), Non-complicated: when the course did not deviate from expected.
[d] Treatment response: treatment with BoNT-A was defined as effective and clinically useful if ≥50% reduction in DQ was found and/or if a reduction of ≥3.86 (2SD) of the VAS score (0–10) occurred at t2 compared to t1. CP, cerebral palsy; y, year; BoNT-A, Botulinum neurotoxin A; t1, baseline; U, unit; DQ, drooling quotient; VAS, visual analogue scale.

Adverse effects

The incidence and characteristics of the adverse effects are listed in Table 2 together with the advices and interventions given post treatment. Adverse effects were recorded in 69 (33%) of the children. Of the 69 children with adverse effects, 22 children (31.9%) experienced saliva swallowing, 51 (73.9%) eating, 22 (31.9%) drinking, 4 (5.8%) articulation, and 15 (21.7%) other problems. In 37 children (53.6%) with any type of adverse effects, an isolated oral motor problem occurred. Simultaneous problems co-occurred in two domains in 23 (33.3%), in three domains in 5 (7.2%), and in four domains in four children (5.8%). Severe adverse effects appeared to be related to the occurrence of multiple problems in one individual at the same time. Of the six children with severe adverse effects, only one child reported one problem, whereas one child experienced two problems, two children three problems, and two children four problems at the same time. In 54 (78.3%) the onset of the adverse effects occurred within 1 week after treatment, while complete disappearance occurred in 37 children (53.6%) before the end of the fourth week post treatment. Two children experienced adverse effects longer than 8 months. The severity of the adverse effects was mild in 55 (79.7%) and no post-treatment intervention was needed in 50 of these children (72.5%). Of the children who experienced severe adverse effects, 4 (5.8%) needed hospital admission or required a substantial change in feeding or a nasogastric tube feed for a few weeks (2.9%). Concerning the phone calls by SLTs and additional outpatient visits, advice involved medication, the adaptation of the food consistency, supportive care, and explanation of the problem (21.7% of the cases). In 76 of the 209 cases (36.4%) saliva became more mucus at t2. Increased viscosity of saliva was positively related to the occurrence of an adverse effect (X^2 [1, n=209]=11.5, p=0.001). No relation was found between the occurrence of adverse effects and being a responder or non-responder to BoNT-A injections at t2 (X^2 [1, n=209]=0.42, p=0.521).

Prediction model

In Table 3, crude ORs and adjusted ORs are given for the biologically plausible risk factors for any adverse effect. The ordinal category with the suspected lowest adverse effect chance was chosen as a reference. Statistically significant predictors of adverse effects were having a diagnosis of CP, higher dosage of BoNT-A, and a pre-treatment drooling quotient below 18%. When all other variables remained stable, children with CP were 3 times more likely to experience an adverse effect (OR: 3.08; 95% CI: 1.53–6.19) than other children. Compared to children injected with <25U Botox, treatment with a dosage of 25U Botox increased the odds of experiencing an adverse effect by a factor 5 (OR: 5.06; 95% CI: 1.07–23.84), whereas children injected with more than 25U Botox were eight times more likely to have an adverse effect (OR: 8.13; 95% CI: 1.02–64.96). Lastly, a pre-treatment drooling quotient <18% increased the odds (OR: 2.40; 95% CI: 1.18–4.88) of developing adverse effects compared with a pre-treatment drooling quotient ≥18%. The AUC of the ROC curve for the multivariable regression analysis was 67% (95% CI: 60–75%).

Table 2: Incidence and characteristics of adverse effects of first botulinum neurotoxin A (BoNT-A) injections in the submandibular glands as well as advices/interventions given post treatment (*n*=209).

	n (%)
A. Incidence of adverse effects	
Adverse effects	
Yes	69 (33.0)
No	140 (67.0)
B. Characteristics of adverse effects (*n*=69)	
Severity of problem[a]	
Mild	55 (79.7)
Moderate	7 (10.1)
Severe	6 (8.7)
Not specified	1 (1.5)
Oral motor problem[b]	
Saliva swallowing problems	22 (31.9)
Eating problems	51 (73.9)
Drinking problems	22 (31.9)
Articulation problems	4 (5.8)
Other	15 (21.7)
Number of co-occurring oral motor problems	
1	37 (53.6)
2	23 (11.0)
3	5 (2.4)
4	4 (1.9)
Time of problem onset	
<1wk	54 (78.3)
1–8wks	5 (7.2)
Unknown	10 (14.5)
Duration of problem	
<1wk	12 (17.4)
1–4wks	25 (36.2)
4–8wks	6 (8.7)
8–32wks	7 (10.2)
>32wks	2 (2.9)
Unknown	17 (24.6)
C. Post treatment advices/interventions	
Interventions	
None	50 (72.5)
Phone consultancy	11 (15.9)
Additional outpatient visit	3 (4.3)
Hospital admission	4 (5.8)
Other[c]	1 (1.5)
Advices	
Start (or increase) of tube feeding	2 (2.9)
Adapt feeding/consistency	9 (13.0
Medication	1 (1.5)
Other	5 (7.2)
None	50 (72.5)
Unknown	2 (2.9)

[a] Mild: short transient changes in saliva swallowing, eating, drinking, or articulation, not leading to changes in lifestyle or doctor visits. Moderate: transient changes in oral motor functions or losing weight, nearly always requiring consultation by a general practitioner. Severe: change in oral motor function requiring one or more days of hospitalization or substantial changes in feeding (e.g. tube feeding).
[b] Multiple problems per child are possible.
[c] Other: combination of advice or interventions.

Discussion

To our knowledge this series represents the largest cohort of children (*n*=209) who received BoNT-A injections exclusively in the submandibular glands. Moreover, our registration of adverse effects was based on a standardized face-to-face contact 8 weeks and 32 weeks post injections. From this study it can be concluded that adverse effects on oral motor functions occur in 33% of the children but, at the same time, that almost

80% of the adverse effects were 'mild' and 54% disappeared within 4 weeks after the injections. By categorizing the oral motor problems after BoNT-A in different domains, we found that eating problems were reported the most, followed by (saliva) swallowing and drinking problems. Only the group of children with moderate and severe adverse effects (*n*=13) needed advice and supervision of the SLT or physician. Considering the pharmacology of BoNT-A, two individuals exhibited unexplained adverse effects lasting longer than 32 weeks, as the normal (median) duration of BoNT efficacy for drooling is 22 weeks.[6]

In previous studies, the incidence of mild or moderate complications of submandibular BoNT injections in children ranged from 0% to 17.8%.[6, 11-13] In the present study we found such complications in 29.7% of the cases, whereas severe adverse effects occurred in 2.9%. Because protocols differed between studies with respect to intervention and follow-up, we estimated the percentages of patients with complications per treatment. Most studies reported complications after combined BoNT injections into the parotid and submandibular glands, or after repeated salivary gland injections in the same individual.[14,16–18] Chan et al.[19] found 15.8% complications after combined injections with major complications in 4% of the cases. In a study by Khan et al., 15 of the 45 patients (33.3%) experienced at least one problem after combined injections. Major problems requiring intensive therapy and prolonged hospitalization occurred in 11.1% of the cases.[14] The adverse effect definition and strict follow-up protocol in our study may be the reason for the relatively high adverse effect percentages. However, it should be noted that some adverse effects in Chan et al.'s [19] study may not have been recognized because of possible recall bias (telephone survey response rate 51%). In conclusion we see fewer severe adverse effects (2.9%) after the two-gland method with isolated submandibular injections than after the four-gland method with combined parotid and submandibular gland injections (4–11.1% complications); this, as also indicated by Gok et al.,[13] would be the first choice in saliva control treatment when BoNT-A injections are considered in children.

Children with CNS disorders who are treated for drooling are vulnerable with regard to their oral motor abilities. In present study, 28.2 to 51.2% already showed dysphagia at baseline. After BoNT-A, the oral motor problems increased in 69 children (33%). As expected, a higher frequency of adverse effects occurred in children with oral feeding skills (87%). Our findings underline the recommendation by Reddihough et al.[1] to regularly contact the patient's caregivers in the weeks after BoNT injections to evaluate oral motor problems.

Authors mentioned two main causes for the deterioration of swallowing and/or speech. Higher salivary viscosity after BoNT-A injections may result in problems with intraoral processing of (solid) food.[20,21] Indeed, we found a significant association between increased salivary viscosity and the occurrence of adverse effects. Concerning oral motor function, the second potential cause of BoNTrelated problems is the diffusion of the toxin outside the salivary gland leading to muscle weakness.[6, 20] The submental muscle group (SMG) plays an important part in normal swallowing.[22,23] After submandibular BoNT, diffusion into the SMG

Table 3: Number of patients with and without adverse effects (AE+/-) and ORs and adjusted ORs with 95% confidence interval based on univariable and multivariable logistic regression analysis with AUC[a] respectively.

Number of patients				
Characteristics	**AE- (*n*=140)**	**AE+ (*n*=69)**	**OR (95% CI)**	**Adjusted OR (95% CI)**
Sex				
Male	81 (57.9)	42 (60.9)	1.00 (reference)	-
Female	59 (42.1)	27 (39.1)	0.88 (0.49–1.59)	-
Developmental age				
<4y	91 (65.0)	40 (58.0)	1.35 (0.75–2.43)	-
≥4y	49 (35.0)	29 (42.0)	1.00 (reference)	-
Diagnosis				
Non CP	61 (43.9)	17 (24.6)	1.00 (reference)	1.00 (reference)
CP	78 (56.1)	52 (75.4)	2.39 (1.26–4.54)	3.08 (1.53–6.19)[b]
Unknown	1			
Degree of mobility				
Ambulant	75 (53.6)	29 (42.0)	1.00 (reference)	-
Non-ambulant	65 (46.4)	40 (58.0)	1.59 (0.89–2.85)	-
Injected dosage BoNT per gland				
<25U	14 (10.2)	2 (2.9)	1.00 (reference)	1.00 (reference)
25U	119 (86.9)	63 (91.3)	3.71 (0.82–16.82)	5.06 (1.07–23.84)[b]
>25U	4 (2.9)	4 (5.8)	7.00 (0.92–53.23)	8.13 (1.02–64.96)[b]
Unknown	3			
Nutrition intake				
Tube/tube and oral	25 (17.9)	9 (13.0)	1.00 (reference)	-
Oral	115 (82.1)	60 (87.0)	1.45 (0.64–3.30)	-
Choking on saliva (t1)				
No	98 (70.5)	47 (72.3)	1.00 (reference)	-
Yes	41 (29.5)	18 (27.7)	0.92 (0.48–1.76)	-
Unknown	1		4	
Choking on food (t1)				
No	77 (55.8)	32 (47.8)	1.00 (reference)	-
Yes	61 (44.2)	35 (52.2)	1.38 (0.77–2.48)	-
Unknown	2		2	
Choking on drinks (t1)				
No	67 (48.6)	32 (47.1)	1.00 (reference)	-
Yes	71 (51.4)	36 (52.9)	1.06 (0.59–1.90)	-
Unknown	2		1	
DQ (t1)				
DQ<18	87	52	1.94 (1.01–3.75)	2.40 (1.18–4.88)[b]
DQ≥18	52	16	1.00 (reference)	1.00 (reference)
Unknown	1	1		

[a] The area under the ROC curve for multivariable logistic regression analysis was 67% (95% CI: 60–75%).
[b] Significant predictors of adverse effects based on multivariable logistic regression analysis. AE+, patients with adverse effects; AE-, patients without adverse effects; OR, odds ratio; –, variables not selected in the multivariable logistic regression analysis.

most likely results in muscle weakness and, as a consequence, the child may not properly control the swallowing process leading to oral dysfunction.

Up to now, it has been unknown which children with CNS disorders will experience adverse effects after BoNT treatment. We tried to discover potential risk factors and identified three clinically significant predictors of the occurrence of adverse effects: diagnosis of CP, higher BoNT-A dosage, and pre-treatment drooling quotient of < 18%.

Children with CP were three times more likely to experience an adverse effect than other children. This finding may be attributed to the fact that, in children with CP, drooling is generally caused by an impaired oropharyngeal swallowing caused by poor oral muscle

control.[3,16] In other children with CNS disorders drooling is usually less associated with motor control, but more commonly caused by less awareness and inability to recognize salivary spill.[17] We hypothesize that, in some children with CP, changes in the viscoelastic properties and the decreased salivary amount, or induced muscle weakness, cannot adequately be compensated by the oral motor system.

In the present study we had the opportunity to compare different dosages of BoNT per submandibular gland. Children treated with 25U and > 25U Botox per gland were more at risk of an adverse effect (5 and 8 times higher risk respectively). Recently, Moller et al.[9] found no relationship between adverse effects and the administered dose or injection method of BoNT-A. Some authors have speculated whether a high volume of liquid or a slower speed of delivery may affect the likelihood of dispersal into surrounding tissues.[18] Currently, the most effective dilution of BoNT and the number of injection sites within the gland are still under debate. Normally, the amount of fluid injected raises the intraglandular pressure and, theoretically, leakage of the drug might occur. Tighe et al.[24] also recently reported dysphagia after BoNT-A extravasation from the glandular puncture site, possibly depending on the injected volume.

At baseline, children who had a drooling quotient < 18 (i.e. mild drooling) were 2.4 times more likely to develop an adverse effect. The drooling quotient is a reliable objective measure of unintentional loss of saliva from the mouth. In a previous study by our team, we concluded that children with a drooling quotient < 18 may be eligible for a more conservative intervention, such as oral sensorimotor training. In cases when those children receive BoNT, because of a failure of the oral motor training and the high impact of the drooling, the mouth could possibly become dry, interfering with mastication. On the other hand, the drooling quotient is a measurement for anterior (visible) drooling and children with a low drooling quotient might be sensitive to posterior drooling, making them more vulnerable to adverse effects – i.e. those children lack the strength to process the thickened saliva making them prone to saliva swallowing problems. We argue that this cut-off threshold should not be applied as the only variable to indicate an invasive treatment. The use of subjective measurements of the severity and impact of drooling on the child and parents should also be encouraged.[15]

Interestingly, we could not find a relation between the occurrence of an adverse effect and being a responder or not. Thus, we are convinced that it is justified to treat children with CNS disorders for chronic drooling because the majority of the adverse effects are mild and will improve within a few weeks in most of the cases.

A limitation of our study is that we focused on a limited set of factors that might influence the occurrence of adverse effects. There may be other risk factors of importance such as the use and/or change of oral medication during/after BoNT treatment. In addition, we did not document any concurrent BoNT injections into the skeletal muscles to treat spasticity. Indeed, disturbances of swallowing and speech have been reported after multilevel intramuscular injections,[25,26] because the total amount of BoNT in the body is

substantially increased after combined intraglandular and intramuscular injections. Thus, clinicians should be aware of the increased risk of oral motor dysfunction if they treat both.

In conclusion, BoNT-A injections can reduce saliva production and constitute one of the treatment options for children with CNS disorders and excessive drooling. However, in one-third of the treatments, mild and transient oral motor problems can be expected. A diagnosis of CP, higher BoNT-A dosage, and mild visible drooling at baseline are associated with an increased risk of oral motor problems. However, more scientific research at both the neurophysiological level (i.e. determinants of the entire pharyngeal swallowing process) and the pharmaceutical level (dose and concentration-finding) is needed. Moreover, such treatment and subsequent follow-up should preferably take place under the responsibility of a multidisciplinary saliva control team that is capable of anticipation and immediate management of adverse effects.

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9

CHAPTER 9

Changes in drooling after submandibular gland botulinum toxin injections in children with neurodevelopmental disabilities: *How to define a meaningful change?*

K. van Hulst
J.J.W. van der Burg
P.H. Jongerius
A.C.H. Geurts
C.E. Erasmus

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Abstract

Aim: To examine changes in objective and subjective drooling severity measures and explore their relationship after submandibular Botulinum Toxin-A injections in children with neurodevelopmental disabilities. To evaluate if clinically relevant response relates to change in impact of drooling.

Method: This longitudinal, observational cohort study involved 160 children (92 males, 3-17 years), treated between 2000-2012 at the Radboud university medical center. Repeated-measures ANOVA was used to compare Drooling Quotient 5 minutes version (DQ5) and Visual Analogue Scale for drooling severity (VAS-$_{DS}$) pre- and post-treatment, and Pearson's rho to assess their association. A parent questionnaire was used to assess the drooling impact in responders (defined as ≥50% reduction of DQ5 and/or ≥2SD reduction of VAS-$_{DS}$ 8 weeks post intervention) and non-responders.

Results: 112 children (70%) were responders. Their mean VAS-$_{DS}$ and DQ5 scores were still significantly lower 32 weeks post intervention compared to baseline. At baseline, the VAS-$_{ds}$ /DQ5-relationship was 'weak' (r_s=0.15, p 0.060), whereas it was 'fair' at 8 (r_s=0.43, p 0.000) and 32 (r_s=0.30, p 0.000) weeks. For responders, a significant change was found in the impact of drooling on daily care and social interaction at 8 weeks after intervention with maintenance of most of these effects at 32 weeks.

Interpretation: A clinically relevant response based on a combination of objective and subjective measures of drooling severity was accompanied by positive changes in drooling impact.

Botulinum toxin type A (BoNT-A) injections in the salivary glands represent an accepted treatment option for drooling in children with cerebral palsy (CP) and other neuro-developmental disabilities. After initial case studies,[1,2] the reduction of salivary flow and its effect on drooling frequency and severity have been documented in cohort studies as well as controlled studies including randomized controlled trials (RCTs).[3-8] In a systematic review, Rodwell et al.[9] concluded that BoNT-A is a temporary effective treatment. Outcomes in these studies included both objective and subjective measures such as flow rate, the Drooling Quotient (DQ),[10,11] Visual Analogue Scales (VAS),[12] the Drooling Frequency and Severity Scale,[13] and the Teacher Drool Scale.[14]

Only a few studies have evaluated changes in the impact of drooling on children and their families. In an RCT, Reid et al.[5] evaluated the effect of BoNT-A injections into the submandibular and parotid glands in 61 children with developmental disabilities. They found a highly significant difference in the mean scores on the Drooling Impact Scale (DrI) between the treatment and control group at one-month follow-up.[5,15] The most significant changes were found in items addressing the severity and frequency of drooling and the number of bibs and clothing changed during a day. They defined non-response to BoNT-A treatment as a reduction of < 10 points on the DrI (100-point scale). In a controlled clinical trial (*n*=45), comparing bilateral submandibular BoNT-A injections to scopolamine treatment, parents reported changes in the impact of drooling up to 24 weeks.[16] Clinically notable responses were found in the frequency that parents wiped the children's chins and changed their bibs, making daily care less demanding. After intervention, the number of parents that reported damage to electronic devices and computers decreased. In addition, social contacts with peers increased. Parents also indicated that the perceived impact of drooling on the child's satisfaction concerning physical appearance, relations within the family and life in general, improved. Since there were only a few parents in this study who observed an overt emotional reaction by the child concerning the impact of drooling, no significant changes in self-esteem could be established in the follow-up period.

Studies on the effect of BoNT-A treatment for drooling in larger groups of children with neurodevelopmental disabilities have become available.[7,17] Unfortunately, alterations in drooling and the possible impact on the daily lives of the children and their parents are mostly not reported.[18]

The saliva control clinic at the Radboud university medical center Nijmegen the Netherlands, has systematically collected objective and subjective measurement outcomes at baseline and after 8 and 32 weeks to evaluate the effectiveness of medical interventions for drooling.

With this study we aim: (1) to examine changes in both objective (Drooling Quotient 5 minutes version (DQ5)) and subjective (VAS drooling severity ($VAS\text{-}_{DS}$)) measures of drooling severity and to explore the relationship between these measures up to 32 weeks after first bilateral submandibular BoNT-A injections in children with CP or other neurodevelopmental disabilities, and (2) to evaluate if a clinically relevant response to treatment (in accordance

with our response definition) is related to parental report of changes in the impact of drooling on daily life.

Method

Inclusion

The flowchart in Figure 1 shows the enrolment and inclusion of participants in this observational study. After standardized assessment of swallowing, children eligible for participation underwent a standardized first-time BoNT-A submandibular treatment (n=160) in the years 2000-2012. Informed consent for BoNT-A treatment was obtained from the child's legal representative(s). The study was conducted in accordance with national and international ethics standards and was approved by the local medical ethical committee (CMO: 2018-4954).

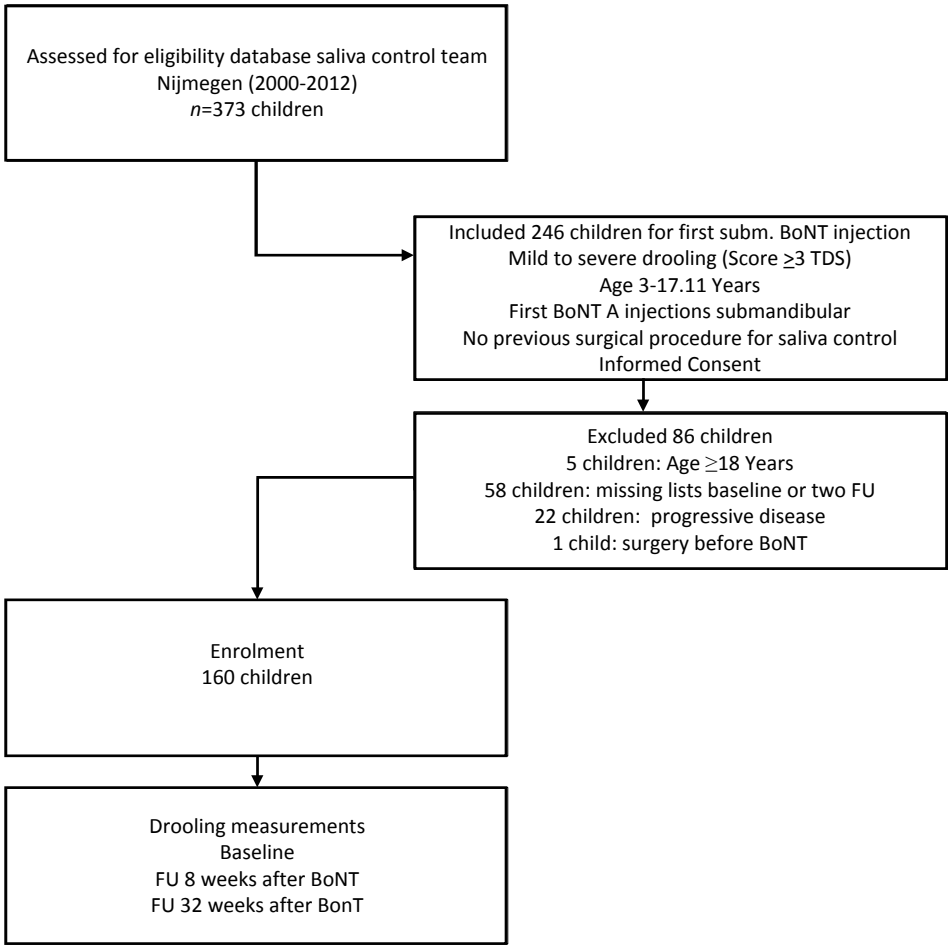


Figure 1. Flowchart of enrolment of participants with Cerebral Palsy (CP) or other neurodevelopmental disabilities.

BoNT-A procedure

Bilateral injections in the submandibular glands with BoNT-A (Botox®; Allergan, the Netherlands) were performed by the same physician (PJ) using ultrasound guidance and general anesthesia. Botox® was diluted in saline 0.9% (25U/ml) and 1 ml was divided over two or three sites throughout the gland using a Spinocan© needle.

Outcome measures

During outpatient visits before injection (baseline) and 8 and 32 weeks after intervention, drooling severity was assessed with the DQ5 and a VAS. The DQ5 was determined by speech language therapists (SLT) of the team and carried out under standardized conditions during an individualized seated activity.[11] During this 5 minute observation, the presence or absence of new saliva was determined at 15 seconds intervals. The DQ5 is expressed as a percentage of observed drooling episodes (intervals with new saliva) and the total number of intervals (0=no new saliva, 100 =100% of the intervals new saliva).

During the three time points, parents also filled in a VAS regarding drooling severity ($VAS\text{-}_{DS}$) (0=no drooling, 100=excessive drooling) and a parent questionnaire (appendix A) on the impact of drooling.[12,19] This questionnaire evaluates the impact of drooling on daily life and care, social interaction and self-esteem.[16] It was developed by our saliva control team[20] and shortened to enhance applicability.[19] Earlier studies have demonstrated that this questionnaire demonstrates the changes in impact after intervention.[12,16,19]

A clinical response was defined as a ≥ 50% reduction of the DQ5 and/or a reduction of ≥ 2 standard deviations of the VAS-DS 8 weeks post intervention compared to baseline.[17]

Data analysis

To evaluate the effects of BoNT-A intervention on drooling severity over time, a repeated-measures ANOVA was used to analyze DQ5 and $VAS\text{-}_{DS}$ scores. Baseline DQ5, and baseline $VAS\text{-}_{DS}$ scores were compared at 8 and 32 weeks, and a comparison was made between 8 and 32 weeks. If the assumption of sphericity had been violated according to Mauchly's test, the Greenhouse-Geisser correction was used. Post-hoc tests were performed to interpret changes that were significant using Bonferroni correction (i.e., p = 0.05/number of tests). The Friedman test was used for nominal and ordinal variables (questions 6-10) to evaluate the effects over time. Also changes in daily care (parent questionnaire: questions 3-4-5) were analyzed by the repeated-measures ANOVA (interval data) for the responder group (RG) and non-responder group (NRG).

To study the correlation between outcomes of the objective (DQ5) and subjective ($VAS\text{-}_{DS}$) measures at baseline and 8 and 32 weeks after intervention, the Pearson's rho was used (0.0-0.25 weak or no relationship; 0.25-0.5 fair relationship; 0.5-0.75 moderate to good relationship; > 0.75 excellent relationship).[21]

To explore different options in evaluating change after BoNT-A treatment, we critically reflected on our response definition and presented the data of the parent questionnaire for two groups.

To describe and analyze data about the impact of drooling on self-esteem (questions 11-14, Appendix A), VAS scores (0= very dissatisfied, 100= very satisfied) concerning satisfaction with respectively 1) 'social contact', 2) 'physical appearance', 3) 'relations within the family' and 4) 'life in general' were re-coded in three categories: 0-32 (dissatisfied), 33-66 (neutral) and 67-100 (satisfied), according to Kok et al.[19] VAS scores for the 'extent to which drooling contributes to the level of satisfaction' (0= not at all, 100= very important) on these four elements were also recoded in three categories: 0-32 (low contribution), 33-66 (neutral) and 67-100 (high contribution). For each question in this section on self-esteem we determined the number of participants that combined dissatisfaction (VAS 0-32) with a high contribution (VAS 67-100) of drooling.

A pooled multiple imputation method (5 iterations) was used to deal with missing values at baseline. To avoid bias in favor of positive outcomes, missing values at 8 or 32 weeks were imputed following a *worst-case-scenario*: a missing value during follow-up was replaced by the baseline value of the participant. If both baseline and follow-up items were missing, no imputation was performed and the participant was omitted from the analysis for that item. Statistical analyses were performed using SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Participants (see also Table 2 in the appendix)

Of the 160 participants, 92 were male. Chronological age at the injection date varied from 3-17 years (M 9y1mo, SD 3y 6mo). All children had neurodevelopmental disabilities, and 123 children (76.9%) were diagnosed with CP (Gross Motor Function Classification System (GMFCS)[22] level: I (n=2); II (n=18); III (n=27); IV (n=33); V (n=43)). Of the non-CP children 31 were ambulant and 6 non-ambulant. Eighty-two children were diagnosed with epilepsy of which 18 had uncontrolled epilepsy. The developmental age (DA) of the children was determined based on prior information from their schools, day centers and/or parents. For 87 children (54.4%) the DA was below 4 years, for 39 children (24%) DA was between 4 and 6 years, and for 28 children (17.5%) DA was above 6 years. Data from 5 children were missing (3.1%). From standardized assessment of swallowing by specialized SLTs, 109 children (69.0%) had oral dysphagia and 49 (31.0%) had oropharyngeal dysphagia. Twelve children (7.5%) were partially dependent on tube feeding, 8 were fully tube-fed and had no oral intake (5.0%), 138 had only oral feeding (86.3%) and for 2 children data about feeding were missing (1.3%). All baseline measures were performed prior to the BoNT-A injections (*M* 2.88mo, *SD* 2.45mo). At baseline, the mean $VAS\text{-}_{DS}$ score was 78.09 (*SD* 17.74) and the mean DQ5 score was 32.43 (*SD* 22.15).

Almost all demographic data in the RG and NRG were comparable. We only found a significant difference in the diagnosis (p 0.013). In the RG (n=112), 80 (71.43%) children were diagnosed with CP, whereas 32 (28.57%) had a different non-progressive neurodevelopmental

disability for example a syndrome or genetic disorder. The NRG (n=48) consisted of 43 children (89.58%) with CP and 5 children (10.42%) with different neurodevelopmental disabilities.

In total, there were 16.6% missing values on the parent questionnaire due to incomplete or incorrect questionnaires. Consequently, there was a difference in the number of children analyzed for different items in the questionnaire. There were no missing values in the DQ5 and VAS-$_{DS}$ measurements.

Clinical response

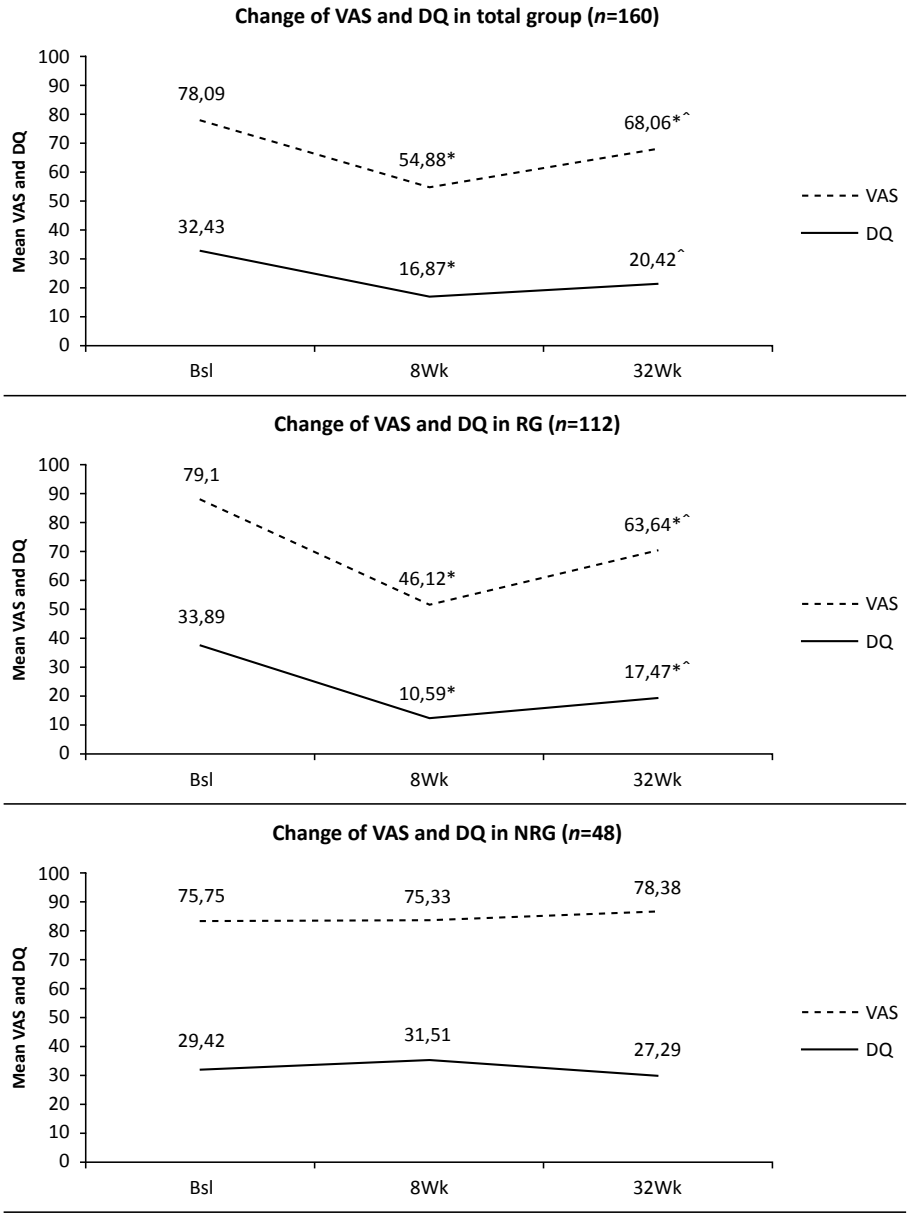
At 8 weeks after BoNT-A injections, 94 children (58.8%) showed a ≥50% reduction in DQ5, while 58 children (36.3%) showed a reduction of 2 SD in VAS-$_{DS}$ from baseline drooling severity. Forty children met both criteria. Applying our clinical response definition, 112 children (70%) experienced a 50% reduction in DQ5 and/or a reduction of 2 SD (2*SD*=35.48) in VAS-$_{DS}$ at 8 weeks after injections. They were considered responders.

Drooling severity: relation between objective and subjective measures

Figure 2a shows the reduction of drooling severity, depicted as both the mean VAS-$_{DS}$ and the mean DQ5-scores for the entire group of participants (n=160) over time. Repeated-measures ANOVA revealed that mean VAS-$_{DS}$ and DQ5 scores differed significantly between time points (VAS-$_{DS}$: F(1.927, 306.382)=48.96, p 0.000), DQ5: F(1.856, 295.136)=54.64, p .000)). Post-hoc tests revealed a significant decrease in both mean VAS-$_{DS}$ (p 0.000) and DQ5 (p 0.000) scores between baseline and 8 weeks follow-up. Between 8 and 32 weeks there was a significant increase in drooling severity for the mean VAS-$_{DS}$ (p 0.000) and DQ5 (p 0.027), although both mean scores at 32 weeks indicated that drooling severity remained significantly below baseline level. Time effects between baseline and 32 weeks were still significant for both measurements: VAS-$_{DS}$ (p 0.000) and DQ5 (p 0.000).

In terms of correlation, there was a 'weak' relationship between VAS-$_{DS}$ and DQ5 at baseline (r_s=0.15, p 0.060). However, at 8 (r_s=0.43, p 0.000) and 32 weeks (r_s=0.30, p 0.000) the relationship was 'fair'.

Figure 2b and 2c outline the changes in drooling severity for the RG and the NRG until 32 weeks. As expected, the RG showed significant differences between the three time points for both VAS-$_{DS}$ (F(2,222)=66.54, p 0.000) and DQ5 (F(1.863,206.743)=92.36, p 0.000). In the NRG, changes between all time points for both VAS-$_{DS}$ (F(1.729,81.242)=0.58, p 0.539) and DQ5 (F(2,94)=1.49, p 0.232) were not significant.



Post-hoc analysis: * significant change between baseline and 8 weeks or between 8 and 32 weeks.
^ significant change between baseline and 32 weeks.

Figure 2. Mean drooling severity based on Visual Analogue Scale (VAS-DS) and Drooling Quotient (DQ5) at baseline (Bsl), and 8 and 32 weeks after submandibular BoNT-A injections in the total group (figure 2a), in the responder group (RG) (figure 2B), and in the non-responder group (NRG) (figure 2C).

Changes in impact of drooling based on the parent questionnaire.

Part 2. Impact of drooling on daily care and economic consequences.

Figure 3 shows the changes in daily care at three points (frequency of mouth wiping (Figure 3a), verbal prompts to swallow (Figure 3b), and bib replacements (Figure 3c)) for the RG and NRG, respectively.

Repeated-measures ANOVA indicated that the frequency of wiping the mouth and chin by parents of responders (n=101) decreased significantly across time (F(1.417, 141.706)=20.43, p 0.000). Post-hoc tests revealed a significant decrease in mouth wiping between baseline and 8 weeks, baseline and 32 weeks, and 8 and 32 weeks follow-up. In the NRG (n=42), no significant changes over time were found regarding the frequency of mouth wiping.

The frequency of verbally prompting the child to swallow in the RG (n=108) decreased significantly from baseline to 32 weeks follow-up (F(1.819, 194.609)=8.07, p 0.001). Post-hoc tests revealed a significant decrease between baseline and 8 weeks after injection, but the scores returned almost to baseline level between 8 and 32 weeks. In the NRG (n=44) no significant changes over time were found for prompting the children to swallow after the intervention.

From baseline to 32 weeks after BoNT-A, a significant decrease in the frequency of replacing the bibs was found in the RG (F(1.443, 160.204)=10.86, p 0.000) and in the NRG (F(1.587,69.822)= 5.39, p 0.011). In the RG (n=112) a significant decrease in replacing the bibs was found between baseline and 8 weeks and baseline and 32 weeks, whereas the change between 8 and 32 weeks was not significant. In the NRG (n=45) only the change between baseline and 8 weeks was significant.

Friedman's test indicated no significant changes in the number of parents in the RG (n=112) that reported damage to computers or other devices during the study(χ^2(2)=5.786, p 0.055). However, in the NRG (n=48) the changes in time were significant (χ^2(2)=9.692, p 0.008) meaning that the number of parents reporting damage to computers or other devices decreased from 15 at baseline, to 6 at 8 weeks and increased to 9 at 32 weeks. In the RG, the number of parents that reported damage to floors and furniture increased significantly (χ^2(2)=11.706, p 0.003; 35 at baseline, 20 at 8 weeks and 22 at 32 weeks), whereas in the NRG these change were not significant (χ^2(2)=3.647, p 0.161).

Part 3. Impact of drooling on social interaction.

Table 1a, illustrates the changes in social consequences for both the RG and the NRG as reported by parents. In the RG there was a significant decrease in the number of parents that reported (a) their child to be avoided by peers because of drooling (χ^2(2)=25.409, p 0.000), (b) being avoided by adults because of drooling (χ^2(2)=7.548, p 0.023), and (c) that the mental ability of their child was underestimated because of drooling (χ^2(2)=12.742, p 0.0002). In the NRG decreases were not significant for all 3 items (a) (χ^2(2)=1.733, p .420), (b) (χ^2(2)=0.667, p 0.717) and (c)(χ^2(2)=4.429, p 0.109).

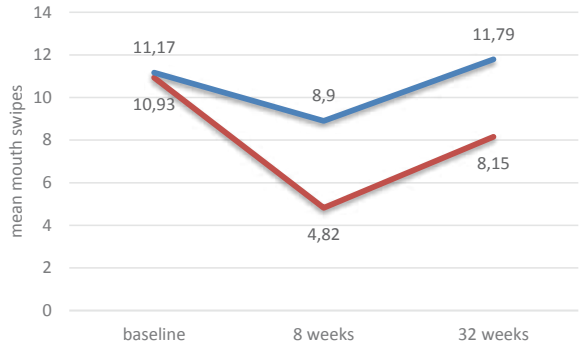


Figure 3a. Mean mouth wiping

NRG (*n*=42)
no significant change before and after BoNT-A ($F(2,82)=2.332$, p 0.104).

RG (*n*=101)
Bsl-8 wks (M=6.11, p 0.000, 95%CI 3.33 – 8.89);
Bsl-32 wks (M=2.78, p 0.000, 95%CI 1.36 – 4.20);
8-32 wks (M=-3.33, p 0.006, 95%CI -5.88 - -.77)

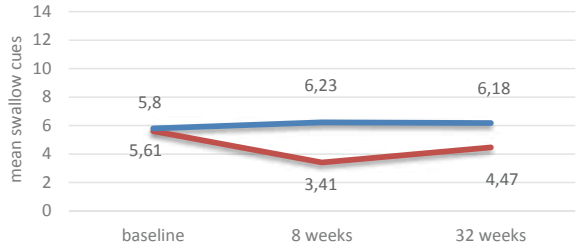


Figure 3b. Mean swallow cues

NRG (*n*=44)
no significant change before and after BoNT-A ($F(1.630, 70.086)=0.12$, p 0.845)

RG (*n*=108)
Bsl-8 wks (M= 2.20, p 0.002, 95%CI .69 – 3.72);
Bsl-32 wks (M=1.14, p 0.054, 95%CI -0.14 – 2.29);
8-32 wks (M=-1.06, p 0.152, 95%CI 2.37 .25)

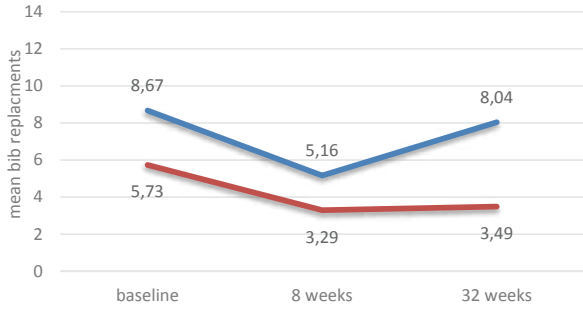


Figure 3c. Mean bib replacement

NRG (*n*=45)
Bsl-8 wks (M=3.51, p 0.02, 95%CI .44-6.58),
Bsl-32 wks (M=.62, p 1.00, 95%CI -1.38-2.63);
8-32 wks (M=-2.89, p 0.10, 95%CI -6.17-.39)

RG (*n*=112)
Bsl-8 wks (M=2.44, p 0.000, 95% CI 1.57-3.31);
Bsl-32 wks (M=2.24, p 0.004, 95%CI .60-3.89);
8-32 wks (M=-.20, p 1.00, 95%CI -1.78-1.39)

Figure 3. Change in impact of drooling on daily care in Non-responders group (NRG) and Responders Group (RG).

Table 1. Social consequences of drooling (part 3), impact on self-esteem (parent impression and emotional reactions of the child, (part 4)) at baseline (Bsl), and at 8 and 32 weeks after BoNT-A in the RG and NRG.

	Responder Group (n,%)			Non-Responder Group (n,%)		
	Bsl	8 Wk	32 Wk	Bsl	8 Wk	32 Wk
a. Social consequences						
Avoided by other children because of drooling (nRG = 112, nNRG = 48*)*	**56(50%)**	**30(27.3)**	**34(30.4)**	**21(43.8)**	**18(37.5)**	**22(45.8)**
Avoided by adults because of drooling (nRG = 112, nNRG = 48)	**38(33.9)**	**26(23.2)**	**29(25.9)**	**15(31.3)**	**13(27.1)**	**14(29.2)**
Underestimation of mental capacity because of drooling (nRG =110/109/109, nNRG =48)	**36(32.7)**	**22(20.2)**	**24(22)**	**10(20.8)**	**15(31.3)**	**16(33.3)**
b. Impact on self-esteem; parent impression[a]						
Dissatisfied about social contact with other children because of drooling (nRG = 102, nNRG = 46)	**3(2.7)**	**1(0.9)**	**2(1.8)**	**3(6.3)**	**3(6.3)**	**1(2.1)**
Dissatisfied about physical appearance because of drooling (nRG = 91/90/89, nNRG = 41)	**2(1.8)**	**1(0.9)**	**4(3.6)**	**2(4.2)**	**3(6.3)**	**2(4.2)**
Dissatisfied about relationships within family because of drooling (nRG = 104, nNRG = 45)	**3(2.7)**	**0(0)**	**1(0.9)**	**2(4.2)**	**1(2.1)**	**0(0)**
Dissatisfied about life in general because of drooling (nRG = 103, nNRG = 46)	**3(2.7)**	**0(0)**	**3(2.7)**	**1(2.1)**	**2(4.2)**	**0(0)**
c. Impact on self-esteem: emotional reactions of child						
Negative about physical appearance because of drooling (nRG = 106, nNRG = 45)	**11(10.4)**	**5(4.7)**	**7(6.6)**	**4(8.9)**	**3(6.7)**	**1(2.2)**
Negative about social acceptance by adults because of drooling (nRG = 103, nNRG = 44)	**5(4.9)**	**1(1)**	**1(1)**	**1(2.3)**	**0(0)**	**3(6.8)**
Negative about peer acceptance because of drooling (nRG = 103, nNRG = 44)	**10(9.7)**	**2(1.9)**	**5(4.9)**	**9(20.5)**	**3(6.8)**	**5(11.4)**

[a]questions 11-14 questionnaire: number and percentage of parents reporting: (1) that their child was dissatisfied (VAS-score 0-32) and (2) that this was related to drooling (VAS 67-100 very important)
nRG = number of children in Responder Group, nNRG= number of children in Non-Responder Group

Part 4. Impact of drooling on emotional development (self-esteem).

Parent impression.

Across the study, only a few parents in both groups reported that their child felt dissatisfied during the past four weeks about social contacts with other children, his/her physical appearance, relations within the family, or his/her life in general because of drooling. Table 1b, shows the numbers and valid percentages for each item. Because of the small numbers of children for whom this was reported, no statistical analysis could be performed. Visual analysis shows a decline in all items in the RG.

Emotional reactions of the child.

Only a small number of children were able to articulate (verbally or with augmentative communication) positive or negative feelings about their appearance and social acceptance by adults or by peers (Table 1c). At 8 weeks, the number of parents in this subgroup that reported negative feelings related to drooling expressed by their child, decreased in both the RG and the NRG. At 32 weeks, the number of parents who reported emotional reactions of their child increased in comparison with 8 weeks. No statistical analysis could be performed because of the small sample size.

Discussion

This study in a group of 160 children with neurodevelopmental disabilities strengthens the findings of previous studies that submandibular BoNT-A injections reduce the severity of drooling. We found a clinical response in 70% of the children at 8 weeks post injection based on our definition. Remarkably, merely a 'fair' correlation was found between the objective and subjective outcome measures at 8 weeks post treatment. Almost 60% of the children showed a reduction of ≥50% of the DQ5. A change of ≥ 2 SD reduction of the parental VAS-$_{DS}$ was found in 36% of the children 8 weeks after BoNT-A injection. Apparently, the subjective opinion of parents with regard to the reduction of drooling severity in daily life did not correspond well with the objective assessment of drooling. This discrepancy between objective and subjective assessments is a striking result of the present study and suggests that both types of assessments do not reflect the same response dimension. Therefore, the DQ5 cannot simply be replaced by the VAS-DS. This conclusion is in contrast with the study of Rashnoo et al.,[23] who found a strong correlation between the objective DQ and a subjective tool, the Drooling Severity and Frequency Scale (DSFS). They suggested that the DSFS and DQ were interchangeable to guide the clinical management of drooling. The results of the current study, however, indicate that a response definition based on a combination of objective and subjective measurements is preferable.

The second aim of this study was to evaluate if a clinically relevant response to BoNT-A treatment was related to the parents' perspectives of meaningful change in the impact

of drooling on daily care, economic consequences, and social and emotional aspects.[12,16] It appeared that BoNT-A injections can make daily care for parents less demanding, as significant decrements in wiping children's mouths and chins, cueing the child to swallow, and bib replacements were demonstrated. The observed group differences in the changes of impact of drooling on daily life between the RG and the NRG seem to support our clinical response definition. Indeed, the decrease in reported frequencies of mouth wiping and prompting the child to swallow was significant for the RG, but not for the NRG. Although the mean amount of bib use was not equally divided between groups at baseline, the mean bib replacement was significantly lower at 32 weeks in the RG, whereas in the NRG it was lower only at 8 weeks post BoNT-A injections. It should be recognized, however, that the frequency of bib changing may not be a sensitive marker of treatment effect, as indicated by Rashnoo et al.[23] who found a rather weak association between the DQ and the number of bib changes. They argued that bib replacement is not sensitive for measuring clinical change after drooling treatment, because parents may change the bib out of habit (e.g., after every meal) rather than to clear dampness. In our opinion, parent behavior regarding bib change will be more related to the severity of drooling as reflected in their VAS-score and not to the DQ-score.

As expected, the results for the social consequences of drooling showed differences between the RG and the NRG: only the parents of the RG group reported that children were less likely to be avoided by other children or adults and to be underestimated with regard to mental capacity. For the emotional consequences of drooling, no substantial changes after BoNT injections could be established in both groups so only tentative conclusions may be drawn.

This may be due to the small number of children who were able to reflect on this important subject: only 28 participants had an estimated developmental age above 6 years.

Not all results were in line with our definition of a good clinical response. For example, in the RG no significant change was found in the number of parents who reported damage to computers or other devices before and after treatment. Surprisingly in the NRG, a significant decrease on this item was found after treatment. No clear explanation could be given for this finding, further research is necessary.

A strength of this observational study is the systematic way in which data were collected in a sample of 160 children. To our knowledge, this study represents the largest cohort of children in which submandibular BoNT injections for drooling is evaluated. All children were systematically selected from a tertiary outpatient clinic and received a first-ever bilateral submandibular BoNT-A injection for drooling, while treatment effect was objectively monitored and parents were asked to fill in questionnaires at baseline, and 8 and 32 weeks after intervention. Our study has several limitations as well. First, SLTs were not blinded during DQ5 observations. Second, the parent questionnaire has not yet been tested on all aspects of reliability and validity, has been shown to be sensitive to change in previous research as well as in the current study.[12,16,19] A favorable aspect of the questionnaire is that

analysis can be done per item, which gives a balanced opinion about (changes in) the impact of drooling on various aspects in daily life. Third, no guarantee could be obtained whether the same parent completed the baseline questionnaire and follow-up questionnaires, which might have affected the response consistency across time. Another limitation is the low developmental age of the children. In our group of participants, 56% of the children had a DA below 4 years. It may have been difficult for parents to report on the social and emotional consequences of drooling for these children. Lastly, with regard to the definition of clinically meaningful change, we acknowledge the limitation of using a dichotomous model of 'responders' versus 'non-responders'.

With reference to the title of this paper, the question was raised: "how to define a meaningful change"? Change basically represents a complicated concept to define as it involves clinical as well as statistical considerations.[24] Change relates closely to the concept of difference that is based on difference scores of measurable entities and in most instances related to a time span. It can be argued that 'change' should primarily be measured on a subjective individual level while making sure that the measurement is objective and accurate. In our response definition, we combined objective (DQ5) and parent-reported subjective (VAS) outcomes for drooling severity. By relating this to parent-reported changes in impact of drooling after BoNT-A injections, we tried to substantiate this definition as reflecting a meaningful change. If we only had used the DQ5 change, there was a risk that relevant post-intervention changes in the home situation would not have been included in the effect evaluation. If we had only used the VAS as an outcome, the basic rules of science that conclusions must be based on objective measurements would have been ignored. Therefore we recommend to use the DQ5, VAS-$_{DS}$ and a parent impact questionnaire in assessing all aspects of drooling. Parent experience of change in drooling severity and its impact after intervention is crucial for their willingness to undetake further treatment. As BoNT-A injection is a temporary effective treatment with a need for general anesthesia, this is an important issue.

The population of children with chronic drooling is very heterogeneous with regard to mental and motor capacities and in our country their social participation ranges from regular and special education to attendance at daycare centers and homes for youth with developmental disabilities. Consequently, the impact of drooling may be different for each individual and his/her relatives. Changes in impact may be valued differently depending on the social and cultural situation within this heterogeneous population. From this perspective, we make a plea for a more personalized approach to the evaluation of drooling, in which meaningfulness of treatment results is considered in the context of the individual's characteristics, circumstances and opinions.

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Table 2. (appendix) Characteristics of participants at baseline (total and RG and NRG) and mean outcomes on DQ5 and VAS-$_{DS}$

Patient characteristics	***n* total**	*(%)*	***n* RG**	*(%)*	***n* NRG**	**(%)**
Sex						
Male	92	(57.5)	62	(55.4)	30	(62.5)
Female	68	(42.5)	50	(44.6)	18	(37.5)
Diagnosis						
CP	123	(76.9)	80	(71.4)	43	(89.6)
Non-CP[a]	37	(37.3)	32	(28.6)	5	(10.4)
Epilepsy						
Absent	77	(48.1)	58	(51.8)	19	(39.6)
Controlled	64	(40.0)	44	(39.3)	20	(41.7)
Uncontrolled	18	(11.3)	9	(8.0)	9	(18.8)
Unknown	1	(0.6)	1	(0.9)	0	
Mental ability						
Developmental age <4 y	87	(54.4)	61	(54.5)	26	(54.2)
Developmental age 4-6y	39	(24.0)	29	(25.9)	11	(22.9)
Developmental age >6 y	28	(17.5)	19	(17.0)	9	(18.8)
Unknown	5	(3.1)	3	(2.7)	2	(4.2)
Degree of mobility						
Ambulant	82	(51.3)	57	(49.1)	23	(48)
Non-ambulant	78	(48.7)	55	(50.9)	25	(52)
Dysphagia						
Oral dysphagia	109	(68.1)	81	(72.3)	28	(58.3)
Oropharyngeal dysphagia	49	(30.6)	29	(25.9)	20	(41.7)
Unknown	2	(1.3)	2	(1.8)	0	
Nutrition intake						
Tube and oral	12	(7.5)	7	(6.3)	5	(10.4)
Tube	8	(5.0)	6	(5.4)	2	(4.2)
Oral	138	(86.3)	97	(86.6)	41	(85.4)
Unknown	2	(1.3)	2	(1.8)	0	
Patient data	**Mean**	*(SD)*	**Mean**	*(SD)*	**Mean**	*(SD)*
Age at inclusion (Y/mo)	9.1	(3.6)	9.4	(3.6)	8.7	(3.4)
DQ5	32.43	(22.15)	33.89	(22.6)	29.42	(20.52)
VAS$_{DS}$	78.09	(17.74)	79.10	(17.1)	75.75	(19.10)

RG= *n*=number, responder group, NRG= non-responder group, CP= cerebral palsy, Y= year. mo=months, DQ5= drooling quotient 5 minutes, VAS$_{SD}$=visual analogue scale drooling severity , *SD*= Standard deviation

[a] Non CP= children with developmental disability mainly as part of a syndrome, genetic, metabolic or neurodegenerative disorder.

[b.] Mobility: Ambulant: Children with CP with GMFCS I,II and III, and ambulant non-CP children. Non-ambulant: Children with CP with GMFCS IV and V, and wheelchair depended non-CP children.

Appendix A: Drooling Questionnaire

Part 1. The severity of drooling in specific daily life situations

1. During the past two weeks the degree of drooling was:
   [----------]
no drooling very severe drooling

2. Mark all conditions in which your child is drooling in the first column. If yes, indicate the degree of drooling for each condition in the past two weeks.

Condition	Degree of drooling				
supported sit	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
unsupported sit	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
prone position	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
walking	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
intensive movement (sports)	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
tired	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
eating	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
drinking	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
talking	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
concentrated activity	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
relaxed, watching TV	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
strenuous activity	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)
enthusiastic	none (1)	mild (2)	moderate (3)	severe (4)	very severe (5)

Part 2. The impact of drooling on daily care and economic consequences

3. How often is his/her mouth or chin wiped dry? …. times per hour

4. How often is he/she told to swallow? …. times per hour

5. How often is his/her bib or shawl replaced? …. times per day

6. Has there been damage to communication aids, electronic communication devices, computer, and/or audio equipment? yes / no

7. Has there been damage to floors and/or furniture? yes / no

Part 3. The impact of drooling on social interaction

8. Did you notice your child being avoided by other children?
0 yes: because of drooling? yes / no / don't know
0 no

9. Did you notice your child being avoided by familiar or unfamiliar adults?
0 yes: because of drooling? yes / no / don't know
0 no

10. Did you notice that familiar or unfamiliar adults underestimate the mental capacity of your child?
0 yes: because of drooling? yes / no / don't know
0 no

Part 4. The impact of drooling on emotional development (self-esteem)

Parent impression

During the past 4 weeks, how satisfied do you think your child has felt about:

11. his/her social contact with other children?

[----------]

very dissatisfied very satisfied

To what extent does drooling contribute to the level of satisfaction of your child in this domain?

[----------]

not at all very important

12. his/her physical appearance?

[----------]

very dissatisfied very satisfied

To what extent does drooling contribute to the level of satisfaction of your child in this domain?

[----------]

not at all very important

13. his/her relations within the family?

[----------]

very dissatisfied very satisfied

To what extent does drooling contribute to the level of satisfaction of your child in this domain?

[----------]

not at all very important

14. his/her life in general?

[----------]

very dissatisfied very satisfied

To what extent does drooling contribute to the level of satisfaction of your child in this domain?

[----------]

not at all very important

Emotional reactions of the child

Although some drooling children cannot express their feelings on the following subjects because of either th age and/or cognitive and/or communication disabilities, we ask you in this section to report only your child's reactions. During the past 4 weeks, did you notice your child expressing any overtly positive and/or negative feelings about:

15. his/her physical appearance?

0 no

0 yes, positive feelings

0 yes, negative feelings: because of drooling? yes / no

16. his/her social acceptance by adults?

0 no

0 yes, positive feelings

0 yes, negative feelings: because of drooling? yes / no

17. his/her social acceptance by peers?

0 no

0 yes, positive feelings

0 yes, negative feelings: because of drooling? yes


10

CHAPTER 10

Summary and General Discussion

Summary

Healthy people are usually unaware of their adaptability in oral motor performance. Essential activities like eating, drinking and saliva control are executed without hesitation and in a smooth way. But for children with neurodevelopmental disabilities, especially for those with cerebral palsy (CP), it is often challenging to chew, drink and swallow in an efficient and safe way. The risk of malfunction in the oral and pharyngeal phase of swallowing as well as the incessant attention needed for oral motor activities have a great impact on the daily life of the child and its caretakers. Inadequate intake of food or serious aspiration of nutrients or saliva will have negative consequences for general health.

In **chapter 1** a general introduction to oral motor performance in children with neurodevelopmental disabilities is presented. The primary goal of the assessment of dysphagia and drooling, and of all possible interventions in this area, is to improve health related quality of life of the children and their caregivers and to enhance meaningful participation. A team approach is recommended and the identified gaps in the assessment of oral motor performance and the management of dysphagia and drooling are described as the inspiration for the research presented in this thesis. In addition, the thesis' outline is delineated in this chapter.

PART I: Towards refined assessment of oral motor performance

Chapter 2 describes saliva control in typically developing children between 0 and 4 years of age. Data was collected by means of a validated parent questionnaire (Drooling Infants and Preschoolers Scale; DRIPS) to quantify drooling frequency and severity. The DRIPS consists of 20 items and was developed to identify severity and frequency of drooling during meaningful daily activities. Sex-specific reference charts were constructed presenting percentile curves for drooling during activities, during feeding, during non nutritive sucking, and during sleep. To illustrate the development of saliva control, eight sex-specific reference curves were constructed to plot the scores of the DRIPS, ordered by age groups, at the 15^{th}, 50^{th}, 85^{th}, and 97^{th} percentiles. About 3–15% of the preschoolers in our cohort did not acquire full saliva control at the age of 4 years.

In **chapter 3** a review is presented concerning swallowing impairments in children with CP. CP is the most common cause of physical disability in childhood with a worldwide prevalence of approximately 2-2.5 per 1000 living births. Children with CP may experience reduced oral motor performance with consequences for swallowing, possibly resulting in severe drooling. Both 'anterior' drooling (visible drooling) and 'posterior' drooling (saliva pooling or saliva aspiration) may occur. A format for the approach to assess and treat swallowing problems in CP is provided.

Chapter 4 summarizes the interrater reliability, construct validity, and usability of the Eating and Drinking Ability Classification System (EDACS) among 149 Dutch children with CP. An officially translated Dutch EDACS version was scored by different speech language therapists (SLTs). Parents also filled out the EDACS scoring forms following the algorithm outlined in figure 1. Usability of EDACS was generally good. Pairs of SLTs as well as parents and SLTs showed good agreement. A strong, significant correlation was found of EDACS with the Dysphagia Management Staging Scale (DMSS). Based on these results, it was concluded that the Dutch version of EDACS is reliable and valid, and can easily be used by SLTs who are either familiar or unfamiliar with the child. Parents of children with CP can also adequately score the Dutch version of the EDACS. Both parents and professionals showed a high level of consistency when classifying eating and drinking abilities. We expect that the use of EDACS can increase the awareness of the safety and efficiency of eating and drinking amongst different stakeholders.

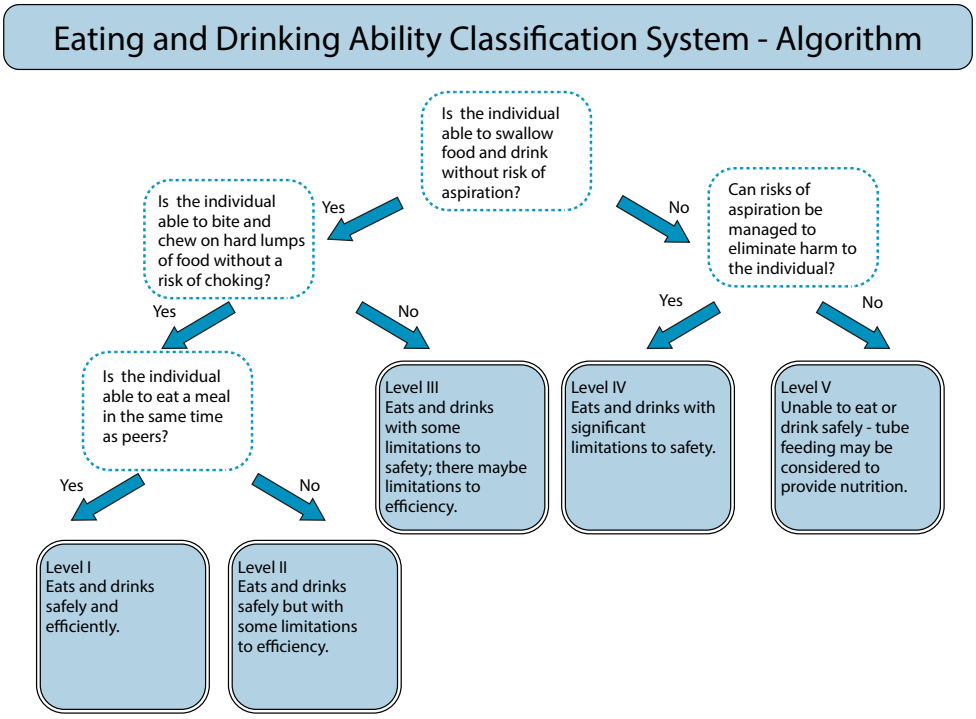

Figure 1. Clinical algorithm EDACS.

In **Chapter 5** we reassessed the 10-minute Drooling Quotient (DQ10) and the 5-minute Drooling Quotient (DQ5) as objective measures of the severity of drooling to evaluate the effects of treatment. No validity or reliability data was available for the DQ10 while from a clinical point of view it would be valuable to reduce scoring time. It appeared that, for clinical and research purposes, the DQ5 is interchangeable with the DQ10 and, thus, time-efficient and cost-saving, while validity, intrarater and interrater reliability are preserved. A cut-off point is suggested to support clinical decision making.

Part II: Towards a personalized approach to the treatment of drooling

The second part of this thesis is dedicated to evidence-informed and customized approaches to treat drooling. Special attention is given to adverse effects on oral motor performance after submandibular botulinum toxin injections and to the clinical response definition of drooling intervention.

In **chapter 6** an international, evidence-informed approach is presented based on the care pathway for sialorrhea of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM). A comprehensive overview of drooling management in children and youth with CP from birth to 25 years of age is described. This chapter includes all levels of evidence to contextualize and guide assessment and treatment regarding oromotor strategies, behavioral therapy, oral appliances, pharmacologic interventions, chemodenervation with botulinum toxin, and surgical treatments for drooling. Flowcharts for assessment and intervention are outlined.

Chapter 7 delineates the personalized management of drooling in children with progressive dystonia (MEGDEL syndrome). The heterogeneity of the cases presented shows the need for stepwise and customized approach in the treatment of drooling.

In **chapter 8** adverse effects on oral motor function after submandibular injections with botulinum toxin for drooling are assessed in 209 children. Transient adverse effects occurred in 33% of the 209 treatments. Almost 80% of these were mild versus 8.7% severe. Approximately 54% of the adverse effects spontaneously resolved within 4 weeks, whereas 3% persisted after 32 weeks. A diagnosis of CP, higher botulinum toxin dosage, and a pre-treatment drooling quotient < 18% were found to be independent predictors of adverse effects. Before using submandibular botulinum toxin injections for drooling, potential adverse effects should be discussed. Oral motor function needs to be monitored, because existing dysphagia may be worsened. The identified clinical predictors could be helpful to optimize patient selection.

In **chapter 9** changes in objective and subjective drooling severity measures are evaluated and their mutual relationship are explored after submandibular injections with botulinum

toxin in 160 children. A clinical response was defined as a ≥ 50% reduction of the (objective) DQ5 and/or a reduction of 2 standard deviations of the (subjective) $VAS_{\text{-droolingseverity}}$ at 8 weeks post intervention compared to baseline. A parent questionnaire was used to assess the drooling impact in responders and non-responders. Results showed that 112 children (70%) were good responders. Their mean $VAS_{\text{-droolingseverity}}$ and DQ5 scores were still significantly lower 32 weeks post intervention compared to baseline. Significant differences in change of drooling impact were present between responders and non-responders. It turned out that a clinically relevant response based on a combination of objective and subjective measures of drooling severity was accompanied by positive changes in drooling impact.

General discussion

The studies in this thesis were intended to refine the assessment of oral motor performance in children with neurodevelopmental disabilities and to develop a personalized approach to the treatment of drooling. This ambition was based on the great challenges that swallow and saliva-control teams are faced with during the process of diagnosing and treating dysphagia and drooling. Over the past 20 years more than 1000 children have visited the academic swallow and saliva-control team of the Radboud university medical center. This experience, previous doctoral research, and the studies presented in this thesis have led to new insights regarding the measurements and treatment of oral motor performance.

Team approach

Dysphagia in children with neurodevelopmental disabilities was the central theme of this thesis. Dysphagia covers difficulties in eating, drinking, and swallowing saliva and may have serious health complications as well as social and emotional consequences. Impaired swallowing is an important focus area for SLTs. SLTs play a central role in the assessment, diagnosis, and treatment of infants and children with swallowing and feeding disorders. As outlined in the national guideline for swallowing disorders,[1] knowledge of and affinity with the patient with dysphagia is necessary for an appropriate process of diagnosing and treatment. Years of clinical practice have shown that clinical experience with adult swallowing disorders does not necessarily qualify an SLT to perform swallowing assessments and interventions in children. Additional knowledge and skills concerning the (developing) anatomy and physiology of swallowing in pediatric populations are needed. Therefore, SLTs who serve the pediatric population at large should be specifically educated and trained. On top of that, a team approach is necessary for correctly diagnosing and managing pediatric feeding and swallowing disorders, as the severity and complexity of these disorders vary widely in pediatric populations.[2] The clinically trained SLT specialized in dysphagia plays a major (and sometimes leading) role in this professional care team.

The pivoting role of the SLT

The SLT is the team member who particularly faces the consequences of a disturbed oral motor performance during eating and drinking and takes care of the daily management of saliva. SLTs have a crucial role in accurate mapping of dysphagia and drooling. From our clinical practice paper regarding swallowing problems in CP (chapter 3), we learned that at an early stage of development particular note should be given to the important impact of dysphagia and drooling. A number of clinical phenomena are closely related to dysphagia (e.g. choking, asphyxiation, motility disorders), which may lead to serious complications (e.g. respiratory tract infections) or long-term health threats such as malnutrition or even mortality. This cascade of consequences stresses the importance of a thorough assessment of all aspects of oral motor performance at an early stage. Existing international consensus states that drooling is a multifactorial problem. In addition, the management of children suffering from dysphagia and drooling requires the coordinated and tailored expertise of an interdisciplinary team.[3, 4] In fact, professionals agree that a personalized approach to the assessment of each child, along with a stepwise approach to the available treatment options, should be pursued. Considering the mission of our swallow and saliva-control team, the ultimate goal is to follow a seamless, interdisciplinary approach to clinical management in which the parents (or legal representatives) and even the child itself are engaged in making clinical decisions. Such an approach must be tailored to the child's needs and unconditionally starts with a thorough assessment by the SLT.

The toolkit of the SLT refined

The crucial role of parents in the assessment of dysphagia

Parents are essential team members who are considered experts of their child's needs. Therefore, their observations form a valuable addition to the toolkit of the SLT. According to the mission of the Radboudumc, family-oriented care primarily concerns improving quality of life and should be centered around the child and its parents and family. Combining the expertise and involvement of the parents with the expertise of a diversity of clinicians leads to meaningful collaboration. Customized goals for assessment and for treatment should preferably be identified by the parents or their child in partnership with the clinical team. Nowadays, it is also widely accepted that parents are indispensably needed to recognize dysphagia.

It is well known that swallow dysfunctions or dysphagia may occur in all phases of the swallowing process and that signs and symptoms may vary based on the phases affected, the child's age, and its developmental level. Because there are a lot of underlying etiologies associated with pediatric feeding and swallowing disorders, clear history taking is important to convert the parental story into professional language, which is needed to communicate among team members. This process of clinical reasoning can be facilitated by the use of the Eating and Drinking Ability Classification System (EDACS). The EDACS can reliably be used

by parents and SLTs as outlined in chapter 4. At the outpatient clinic, the classification of EDACS level by both the SLT and the parents forms the basis for discussing the safety and efficiency of the child's eating and drinking. Most parents of children with CP are familiar with the system of the Gross Motor Function Classification System (GMFCS) and know the GMFCS-level of mobility of their child. Given the fact that the EDACS and the GMFCS have only a moderate (positive) association, parents and professionals should be aware that these levels are not interchangeable. Considering that the EDACS exclusively describes the *performance* of eating and drinking, and not the *capacity* of the child, parents need to be closely involved in classifying the efficiency and safety during daily feeding situations. Discrepancies between the opinion of the SLT and parents should be discussed and are important for sufficient comprehension of the oral motor performance of the child during eating and drinking. The outcome of the discussion has implications for the therapeutic approach. In general, children with EDACS levels I and II present problems in the oral phase of swallowing. Children classified as EDACS level III typically have additional problems in the pharyngeal phase of swallowing, whereas children with EDACS levels IV and V have severe (oro)pharyngeal problems. The EDACS provides direction with regard to swallowing capacity and the possible existence of dysphagia.

The crucial role of parents in the assessment of drooling

Apart from the assessment of dysphagia, the existence and severity of (possible) drooling should be assessed. Next to the SLT's judgment of drooling severity, it is important to ask parents about the impact and consequences of drooling in their own lives and the life of their child. With regard to treatment effect, no internationally accepted clinical response definition exists. Therefore, our swallow and saliva-control team has proposed a definition of clinical response combining an objective (quantitative) with a subjective (semi-quantitative) criterion (i.e., ≥ 50% reduction of the objective DQ5 and/or a reduction of 2 SD of the subjective $VAS_{\text{-severity}}$ at 8 weeks after intervention). In addition, a parental questionnaire is used comprising questions regarding the severity of drooling in daily situations and the impact of drooling on daily care, costs, social interactions, self-esteem, and emotional reactions of the child.

In chapter 9 we showed that there was a discrepancy in response between objective (measurement scales) and subjective (parental information) measurements of drooling severity after botulinum toxin injections in the submandibular glands. An explanation for this discrepancy may be that both types of assessments do not reflect the same response dimension. This 'response disparity' forces clinicians to approach the consequences and the impact of drooling in a more individual manner, tailored to the families of the drooling child. Even more, a balanced management of outcome expectations by the parents with respect to their cultural values has to be addressed at an early stage (pre-treatment) after first contact with the team. The question arises whether there can ever be a single approach that can be applied generically, taking into account the enormous variation in socio-cultural

backgrounds. To achieve this, an assessment is needed that reflects both the individual performance and the (parents') satisfaction with drooling treatment. For this purpose, a new outcome measure, based on the Canadian Occupational Performance Measure (COPM),[4] has been developed and used by our team.[5] This so called Measure of Performance and Satisfaction for Saliva Control ($MPS_{saliva\ control}$) requires parents to identify five daily activities that are important to their child in which saliva spill is most problematic. The outcomes allow to calculate difference scores with regard to both the performance of and satisfaction with these activities before and after treatment. The experiences with the introduction of the $MPS_{saliva\ control}$ support our philosophy that parents are valuable team members and have strengthened our expectation that the $MPS_{saliva\ control}$ is a promising addition to the existing instruments. However, further research is needed to determine the true value and position of the $MPS_{saliva\ control}$ in the field of drooling interventions.

Assessment of the preschooler

From the neonatal period up to a certain age, drooling can be regarded as normal. Although there is discussion among professionals about the minimum age at which children should be referred to an interdisciplinary saliva-control team, the policy in our team is to examine the children from the age of four years. Nowadays, however, SLTs experience an increasing number of questions and concerns from parents of younger children. In general, parents become worried when the severity and frequency of drooling seems to be more than in peers. Indeed, the normal intensity of drooling in children under the age of four is repeatedly subject to debate. Therefore, we developed a parental questionnaire abbreviated as DRIPS (Drooling Infants and Preschoolers Scale), and validated this scale to fill this gap (chapter 2). Although in the literature it is generally accepted that drooling ceases after the age of four years, our study provided evidence that a substantial part of the typically developing preschoolers (3-15%) are still drooling to a certain extent at four years of age. Hence, the question arises from what age drooling has to be considered as pathological. The answer to this question is crucial for saliva-control teams and formed the basis to develop an evidence-based algorithm for the treatment of drooling (this chapter). Based on the results of the DRIPS study, we suggest to use the 97^{th} percentile on the DRIPS charts as the cut-off value for pathological drooling and to consider DRIPS scores above the 85^{th} percentile as an indication of deviated saliva control. In both these instances, children should be referred to an SLT for oral motor therapy.

The use of the DRIPS essentially changed the approach of our saliva control team and, more generally, the referral to SLTs for further treatment. When children below the age of four years are referred to our team, parents are advised to fill out the DRIPS. Based on the DRIPS scores and charts a personalized approach is taken. When the percentile score is below the 85th percentile no treatment will be started, but it is advised to the primary-care SLT to monitor the child by means of the DRIPS (parental questionnaire) every three months. When the percentile scores of one or more DRIPS factors is above 85, oral motor treatment

by specially trained SLTs is advised. In the Netherlands, recently developed workshops are available to instruct SLTs to assess and interpret the individual DRIPS profiles. In the age group under four years, only children that present with symptoms of posterior drooling (not visible dripping, saliva aspirations) are encouraged to consult our saliva-control outpatient clinic.

Assessment of dysphagia and drooling

After optimizing any neurological dysfunction (in particular dysfunctions of the brain-gut axis) (chapters 3 and 7), the SLT focuses on the clinical evaluation of swallowing, the impact of dysphagia on general health, and the impact of swallowing and feeding impairments on quality of life. One of the first steps in the clinical evaluation of oral motor performance is to determine what contributing conditions cause the child to drool and whether the child aspirates during feeding, aspirates saliva (posterior drooling), or spills saliva from the mouth (anterior drooling). The distinction between anterior and posterior drooling is important because both problems need their own approach as shown in figure 2 in this chapter.

In children with CP, a close connection can be expected between drooling and aspiration of saliva and food.[6] Drooling often occurs simultaneously with eating and drinking problems, because all of these problems are related to dysfunctions in the oral and oropharyngeal phases of swallowing. Thus, a close relationship between eating and drinking ability, dysphagia, and drooling is likely, although the literature to support this relationship is still scarce. Based on a study by Tas et al.[7], a significant difference of eating and drinking abilities was found between a group of CP children who drooled and a group who did not. They were able to establish that when head control improves, drooling severity diminishes. They also showed that drooling severity increased with decreasing body-mass index. This could be explained by the fact that children who experience saliva and food loss are at greater risk of malnutrition due to their disturbed oral motor performance. Generally, they determined that drooling affected nutrition and that drooling control was affected by head control. The notion that drooling affects nutrition is corroborated by the results of our study regarding the adverse effects of submandibular botulinum toxin injections for drooling (chapter 8). We found that existing swallowing problems (e.g. choking on drinks, food or saliva) increased in 88% of the children who experienced adverse effects after treatment (33%) which shows the vulnerability of the oral motor system. If the EDACS classification gives rise to doubts about the safety of swallowing, it is essential to investigate efficiency and safety of swallowing with an objective evaluation prior to drooling treatment. Instrumented evaluation by videofluoroscopy or fiberoptic endoscopy of swallowing (FEES) may be indicated for children with neurodisabilities if further information is needed to determine the nature of the swallowing disorder. Instrumented evaluation can also help to find out if swallow safety can be improved by modifying food texture, liquid consistency, volume and rate of feeding, or positioning.

Most of the quantitative scales for children with anterior drooling were not designed to measure posterior drooling. In patients with posterior drooling, practitioners are typically dependent on clinical information to assess drooling severity such as signs and symptoms of recurrent respiratory tract infections, number of episodes of respiratory infections and antibiotic use, history of chronic lung disease, and the need for frequent suctioning. Because posterior drooling is often suspected in children with severe oropharyngeal dysphagia, we developed and piloted the Pediatric Posterior Drooling Scale (PPDS).[8] The PPDS is a new screening tool to score the presence and severity of posterior drooling with the use of cervical auscultation. The PPDS scores the quality of breathing and swallowing using a 5-point scale. Previous research has shown that cervical auscultation may be used to evaluate post-swallow respiration.[9-11] The PPDS can be scored reliably by experienced SLTs and may be an appropriate screening tool to score the presence and severity of posterior drooling in children with central neurological disorders. It can also be used to evaluate interventions for posterior drooling. However, further research has to be done to definitively establish the reliability and validity of the scale in a larger population. Until then, we use the PPDS as a screening instrument to measure the effect of a drooling intervention on saliva pooling before and after treatment. The diagnostic position of the PPDS is illustrated in figure 1 of chapter 6.

In contrast, the severity of anterior drooling can be assessed with a range of objective and subjective measures. Quantifying the severity and frequency of drooling is important, particularly because it allows for tracking of symptoms during consecutive interventions. The shortened version of the drooling quotient (DQ5) is proven to be reliable (chapter 5) and the DQ5 during daily activities appears to be the objective measure of choice for use in clinical practice and research. A cut-off point has been introduced that could serve as a 'rule of thumb' for decision-making in drooling treatment. A DQ ≥ 18% means that the drooling problem is frequent and/or has not been satisfactorily resolved by previous treatment. This cut-off point is useful in clinical decision making. Children with a DQ < 18% may be eligible for more conservative treatment, such as oral motor training or behavioral therapy. In children with a higher score (DQ ≥ 18%), invasive interventions such as botulinum toxin injections or surgery may be the therapy of choice, combined with oral motor treatment or behavioral therapy. In one of our studies on the adverse effects of submandibular botulinum toxin injections (chapter 8) we also found that the cut-off DQ point(< 18%) is one of the independent predictors of adverse effects. Children with a pre-treatment DQ < 18% are more likely to experience adverse effects than children with a higher pre-treatment DQ. This could be explained in two ways: children with a DQ < 18% may experience too much dryness of the mouth after treatment, which interferes with mastication, or children with a DQ < 18% are more likely to suffer from posterior drooling. Overall, it is possible that children have more problems to process the reduced but thickened saliva after treatment,[12] as their oral motor dysfunction makes them vulnerable to adverse effects. These results underline the need of a precise and accurate pre-treatment oral motor performance assessment. Obviously, our

team does not use this cut-off point as the only indicator of the need for invasive treatment, as we argue that a combination of objective and subjective measurements is preferable to decide if and what treatment is necessary and to evaluate treatment effects.

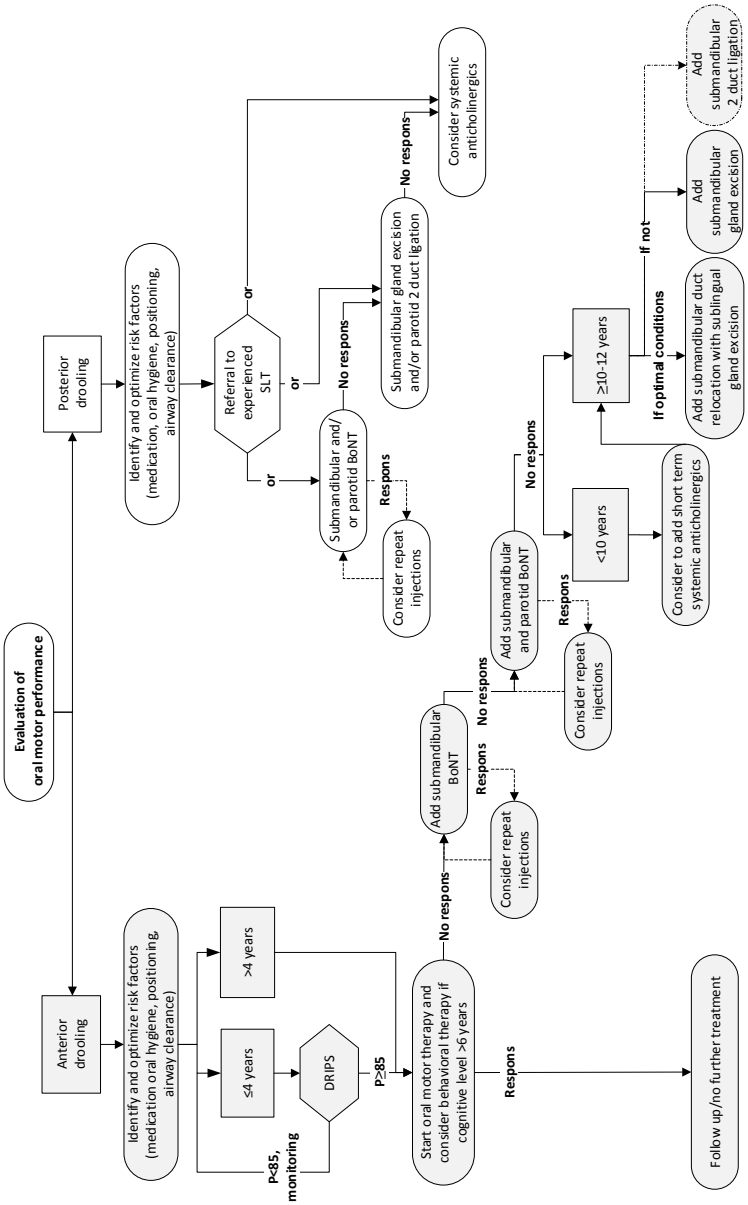

Figure 2. A stepwise approach to the clinical management of drooling at the Amalia children's hospital of the Radboud university medical center, Nijmegen, the Netherlands.

Legend: DRIPS= Drooling Infant and Preschoolers Scale, P= Percentile, BoNT = Botulinum Toxin -A

A stepwise approach to the clinical management of drooling

The flowchart outlined in figure 2 is based on the results of this thesis as well as on previous research from our swallow and saliva-control team and starts with a solid assessment of oral motor performance to decide which treatment option is most appropriate for an individual child in a specific developmental stage. Several differences in treatment approaches became apparent when our team collaborated with an international peer group to construct a care pathway for sialorrhea (drooling) for the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM)[13] (chapter 6). The current literature did not allow the development of a uniform evidence-based worldwide guideline for the clinical management of drooling. Therefore, the review in chapter 6 does not delineate a specific order of interventions for drooling, but highlights the treatment options as well as the published evidence for each intervention. Global differences in approach were found regarding the age at which interventions should take place, the treatment sequence or treatment choice.

Global similarities and differences in drooling treatment

In most teams abroad, oral motor therapy is seen as the first mandatory step in the treatment of drooling. However, we argue that oral motor therapy should only be considered after identifying and optimizing risk factors which may exacerbate drooling (e.g. incomplete oral health, inadequate posture and positioning, head instability, malocclusion, airway obstruction, excessive mouthing). Our clinical experience suggests that oral motor therapy is most effective in children with mild to moderate oral dysfunction and good cognitive skills, who are highly motivated to improve their drooling.[14] With the recently developed DRIPS, teams are able to monitor drooling in infants and preschoolers under the age of four years using the parental questionnaire and the charts. Based on this assessment, a customized advice to improve factors responsible for the lack of saliva control can be given. More research is necessary to develop an evidence-based oral motor treatment for older children.

In the international literature, most studies on behavioral intervention apply techniques for external control of antecedents and consequents of drooling (i.e. instruction, cues and feedback from people or devices) with the risk of an increase of drooling after the intervention procedure is stopped. The development and implementation of a self-management program for drooling was reported by our team and attracts worldwide interest.[15, 16] This program aims to teach self-management skills (internal control) to the child with anterior drooling in order to improve the frequency of swallowing and/or wiping the mouth and chin and teach the child to monitor salvia control.[15] The program is suited for children with a mental developmental age above 6 years and intrinsic motivation to remain dry. Children also must be able to swallow on request before the start of a self-management program. That is why oral motor therapy to teach active swallowing often is advised before the start of behavioral intervention.

There is a large variation worldwide with respect to the earliest age at which treatment with botulinum toxin is offered. Since 2001, such injections were described by Jongerius et al. as a new treatment option for drooling in children with CP.[17] At present, the minimum age for botulinum toxin treatment in the Netherlands is four years, with an exception for younger children who suffer from posterior drooling and who need urgent treatment to prevent saliva aspiration.[18] The reason for applying a minimum age in our team is supported by the DRIPS study.[19] Nowadays, we are able to monitor saliva control under the age of four years, so that we can treat preschoolers based on their specific drooling profile. Other teams sometimes inject children with anterior drooling around the age of two years.

Although there is an international consensus statement on the treatment of drooling with botulinum toxin injections,[3] no consensus exists as to which salivary glands should be injected in first instance. The submandibular glands are responsible for the majority of salivary production at rest, whereas the parotid glands are mainly functional during mastication and digestion of food. Thus, when botulinum toxin injections are indicated, our team decided to start with injecting the submandibular glands only. It was expected that injections in the submandibular glands would sufficiently diminish salivary flow to reduce drooling, whilst preserving saliva excretion by the parotid glands during eating and drinking. This last aspect is particularly important for children with dysphagia. Although some authors share our policy, in many countries it is common to inject both the submandibular and parotid glands as the first step in the treatment of drooling with botulinum toxin. This approach may, however, imply overtreatment since previous studies[18, 20] and the research reported in chapter 9 have shown that there is a large proportion of children that sufficiently respond to submandibular gland injections alone. Hence, we argue that submandibular gland injections are satisfactorily effective if patients are carefully selected and receive an adequate follow-up. Due to their temporary effect, botulinum toxin injections need to be repeated if the child appears to be a responder at follow-up. When there is no (or an unsatisfying) response, the parotid glands may still be injected in second instance, along with the submandibular glands. Because the parotid glands are mainly active following tactile and gustatory stimulation, the SLT has to judge the food consistency and the swallow and chewing capacities of the child before treatment of these glands with botulinum toxin. In addition, parents should be given specific advice for the period following this intervention.

Various surgical options exist for the treatment of drooling. Generally, our team offers surgery to children above the age of 10 years, as we want to await the development of oral motor skills and growth of the mouth area. Submandibular duct relocation combined with excision of the sublingual glands is considered to be the most effective intervention by all saliva-control teams. There is an attractive physiological principal underlying this type of surgery. It's aim is not to diminish salivary flow, but to relocate the ducts of the submandibular glands towards the base of the tongue where saliva is triggering the swallow reflex. This treatment option is, however, only possible in children with a safe pharyngeal swallow function and without posterior drooling, which is why prior to intervention a

thorough oral motor assessment is needed. Our team has proven that submandibular duct relocation combined with excision of the sublingual glands appears to be safe and effective in diminishing visible drooling in children with neurological disorders, particularly in children aged 12 years or older with a safe pharyngeal swallow function and without a protracted head position.[21] In contrast, bilateral submandibular gland excision is the procedure of choice in children with neurological disorders who drool due to severe dysphagia, in whom submandibular duct relocation is contraindicated. A previous study of our team showed that drooling intensity was significantly reduced compared to baseline following this type of surgery.[22]

Recently, a randomized controlled trial has been conducted in which botulinum toxin treatment of the submandibular glands was compared with bilateral submandibular duct ligation (2-DL).[23] This study suggested that 2-DL could be an effective follow- up therapy after botulinum toxin treatment, since 2-DL proved to be more effective for drooling reduction than the use of botulinum toxin. The exact position of 2-DL in the treatment of drooling has yet to be determined.

Another difference in treatment approach between our team and other saliva-control teams worldwide is the use of anticholinergic medication. Currently, there is evidence that glycopyrrolate is recommended (before scopolamine) as a first-line pharmacological agent for anterior drooling in children with CP.[24] However, in our team we are reluctant to prescribe anticholinergic drugs because of their side effects and because published safety data are not yet available beyond 24 weeks treatment duration. As stated by the European Medicine Agency (EMA), total treatment duration should be kept as short as possible, given the limited long-term safety data available and the uncertainties about the potential carcinogenicity of anticholinergic drugs. We believe that, only if no other treatment is effective and anesthesia brings about too great a risk, anticholinergic drugs may be used to treat drooling, provided that the side effects are carefully monitored. The most disturbing side effect of anticholinergic medication, just as of botulinum toxin, is thickening of saliva. This is the reason why, in the process of deciding how to reduce (the impact of) drooling, the adverse effects of these treatments on mastication and swallowing should be considered.

Future research

Despite scientific developments, dysphagia and drooling remain extremely challenging clinical problems, particularly in (young) children with neurological disabilities. From this perspective, a strong case can be made for a mechanism-based and, at the same time, personalized treatment approach. Such an approach requires the unraveling of the pathophysiology of dysphagia and drooling in detail. For instance, there is still little insight in why one child with CP drools and the other child with exactly the same type and severity of CP does not. ‘Unawareness to swallow’ is often taken as an explanation. However, to improve and develop mechanism-based therapies for drooling, more knowledge is

essential. For instance, one can train 'awareness of drooling' only if there is adequate sensibility, whereas one must learn compensatory tricks (e.g. performing visual checks in the mirror) if there is lack of sensibility. In our clinical practice, we notice children with saliva loss who are unresponsive to the feeling of getting a wet chin. Because sensibility testing is challenging and maybe unreliable in this group of children, we intend to conduct a pilot study with short- and long-latency Somato Sensory Evoked Potentials (SSEP) to investigate the relationship between drooling and oral sensation. Another way to get insight in the mechanisms underlying dysphagia is the use of ultrasound to assess the quality of the muscles involved in the swallowing process, like van den Engel-Hoek et al. suggested.[25, 26]

Moreover, it is necessary to improve the clinical usefulness and accuracy of the DRIPS and the EDACS. Cross-sectional data have been acquired in the DRIPS study, but a longitudinal study still needs to be conducted. Future research should preferably investigate long-term data on saliva control in typically developing children as well as in children with pathological saliva loss. Looking back critically at the process of developing the DRIPS, it would have been of value to widen the inclusion of participants up to six years of age, because it turned out that some of the typically developing children still lose saliva at four years of age. Furthermore, the relationship of the EDACS score with drooling has not yet been elucidated. We hypothesize that children with EDACS levels I, II or III are most likely to suffer from anterior drooling, whereas children classified as EDACS level IV or V are more likely to show posterior drooling. A related challenge is to investigate the relationship between EDACS level and nutritional status in order to improve health related feeding issues. This is something to look at in a natural history study.

The existing global differences in the use of botulinum toxin also emphasize the need for further clinical studies in this area. At the moment, our team advices bilateral injections into the submandibular glands as a first step, followed by combined injections into the four major salivary glands (bilateral submandibular and parotid glands) as a second step to manage drooling. To determine if the *'foreign'* (combined) approach might be more effective, we intend to conduct a comparative study and, at the same time, examine the characteristics of non-responders to improve treatment selection.

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Appendices

Nederlandse samenvatting

Gezonde mensen zijn zich meestal niet bewust hoe vanzelfsprekend en gemakkelijk zij eten, drinken en (speeksel) slikken. Op het moment dat de mondmotorische uitvoering 'even' moeizaam verloopt kunnen zij zich aanpassen door bijvoorbeeld de hap wat langer in de mond te houden, de hap beter te kauwen, een kleinere slok te nemen of desnoods het eten of speeksel uit te spugen. Dit aanpassingsvermogen hebben kinderen met neurologische ontwikkelingsproblemen niet. Dit geldt in het bijzonder voor kinderen met Cerebrale Parese (CP) of kinderen met ernstig meervoudige beperkingen (EMB). Voor hen is het een uitdaging om te kauwen, drinken en slikken op een efficiënte en veilige manier. Het risico op slikproblemen in de orale (mond) en/of faryngeale (keel) fase, en de constante aandacht die nodig is voor het veilig en efficiënt eten en drinken, hebben grote impact op het dagelijkse leven voor zowel het kind als de verzorgers. Onvoldoende intake van voedingsstoffen of ernstige aspiratie (verslikken) van voeding of speeksel kan negatieve consequenties hebben voor de algehele gezondheid van het kind.

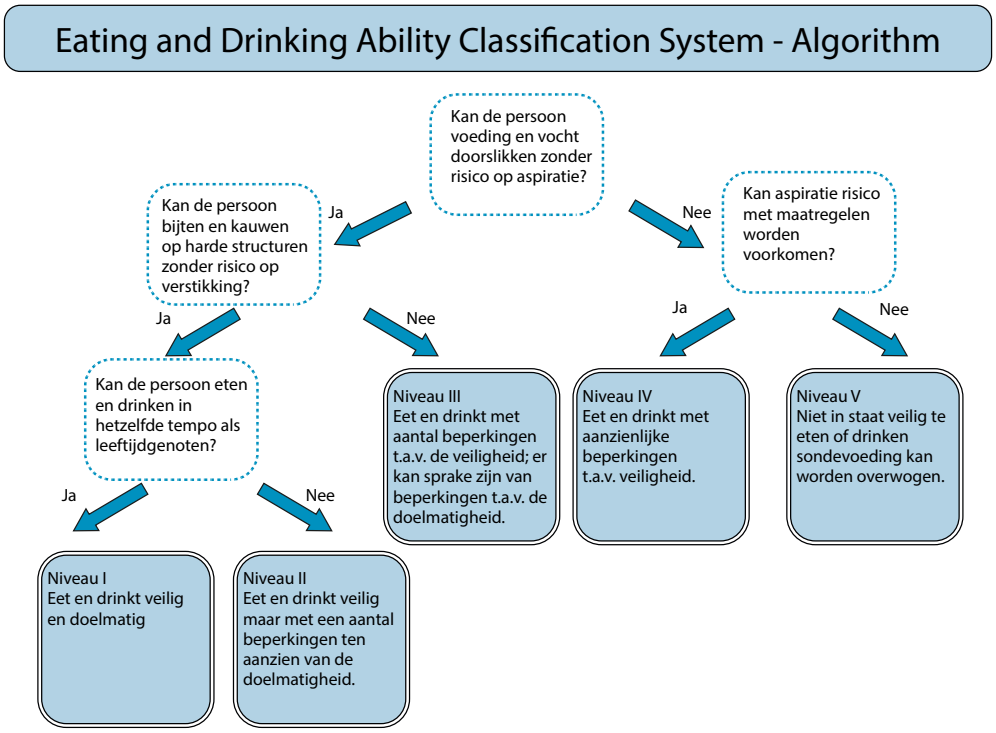
Hoofdstuk 1 bevat een algemene introductie over 'oral motor performance' (de uitvoer van oraal motorische bewegingen voor bijvoorbeeld slikken en speekselcontrole) waarin wordt gerefereerd aan de moeilijkheden die kinderen met neurologische ontwikkelingsproblemen zoals CP, kunnen hebben bij de uitvoering van mondmotorische vaardigheden in het dagelijks leven (eten, drinken, slikken en speekselcontrole). De eet-, drink- en slikproblemen hangen vaak samen met de gestoorde mondmotoriek, een abnormale neurologische rijping en aansturing en houdings- en bewegingsstoornissen. Gedegen diagnostische onderzoek naar slikstoornissen (dysfagie) en speekselverlies (drooling) is belangrijk voor de juiste interventie. Het primaire doel is dan ook om de gezondheidsgerelateerde kwaliteit van leven, voor zowel het kind als de verzorgers, te verbeteren zodat participatie in het dagelijks leven wordt vergemakkelijkt. In verband met de complexe problematiek van deze kinderen wordt een teambenadering aanbevolen voor het onderzoeken en behandelen van de kinderen. In de introductie wordt een beschrijving gegeven van bestaande diagnostische instrumenten en de geconstateerde hiaten in het onderzoek naar 'oral motor performance'. De gevonden hiaten vormden de basis van de studies die worden gepresenteerd in deel I van dit proefschrift. De behandeling van speekselverlies heeft als doel om het zichtbare speekselverlies (anterior drooling) te doen afnemen maar ook om het verslikken in speeksel (posterior drooling) te verminderen, zodat het leven van het kind en de verzorgers aangenamer wordt. Sinds 2001 hebben verschillende leden van het slik- en speekselcontroleteam hun PhD project afgerond en zijn er vele studies verricht naar dysfagie en de behandelaspecten van speekselverlies. Hoewel significante vooruitgang is geboekt in de behandeling van speekselverlies bij kinderen met neurologische ontwikkelingsstoornissen, zijn er nog steeds substantiële hiaten in onze kennis over de manier waarop het onderzoek en de behandeling op maat moet zijn voor ieder kind. Het tweede deel van dit proefschrift is dan ook gewijd aan het

ontwikkelen van een evidence informed (op bewijs gestoelde) en kindspecifieke benadering van de behandeling van speekselverlies. Er wordt met name aandacht besteed aan de nadelige effecten van Botuline Toxine A injecties in de speekselklieren op de 'oral motor performance'. Tevens wordt de klinische responsdefinitie zoals gehanteerd binnen onze klinische en research praktijk geëvalueerd.

In **hoofdstuk 2** wordt een beschrijving gegeven van de ontwikkeling van speekselcontrole bij normaal ontwikkelende kinderen tussen 0 en 4 jaar, gebaseerd op gegevens van 652 vragenlijsten. Om de ernst en frequentie van het speekselverlies te kwantificeren werden gegevens verzameld door middel van een gevalideerde oudervragenlijst (Drooling Infants and Prescoolers Scale; DRIPS). De DRIPS bestaat uit 20 items en is ontwikkeld om de ernst en frequentie van het speekselverlies te identificeren gedurende dagelijkse activiteiten. Geslachtspecifieke referentiegrafieken zijn samengesteld met percentielcurves voor de mate van speekselverlies tijdens activiteiten, eten en drinken, niet voedend zuigen (speen of duim) en tijdens slaap. Om de ontwikkeling van speekselcontrole te illustreren worden er 8 specifieke referentiegrafieken gepresenteerd waar de scores van de DRIPS, per leeftijdsgroep, kunnen worden afgezet tegen de 15e, 50e, 85e en 96e percentiel lijnen. Tussen de 3-15% van de kleuters in het cohort had nog geen volledige speekselcontrole bereikt op de leeftijd van 4 jaar.

In **hoofdstuk 3** wordt een overzicht (review) gepresenteerd betreffende slikstoornissen bij kinderen met cerebrale parese. CP is de meest voorkomende oorzaak van motorische beperkingen bij kinderen met een wereldwijde prevalentie van ongeveer 2 tot 2,5 per 1000 levend geboren kinderen. Kinderen met CP hebben vaak een beperkte 'oral motor performance' met gevolgen voor het slikken, soms resulterend in (ernstig) speekselverlies. Zowel anterieur speekselverlies (zichtbaar speekselverlies uit de mond), als ook posterieur speekselverlies (speekselstase in de keel of speekselaspiratie) kunnen voorkomen. Een opzet voor de wijze waarop slikproblemen bij CP kunnen worden onderzocht of behandeld wordt voorgesteld.

Hoofdstuk 4 beschrijft het onderzoek naar de interbeoordelaarsbetrouwbaarheid, de construct validiteit en de gebruiksvriendelijkheid van het Eating and Drinking Ability Classification System (EDACS) bij 149 Nederlandse kinderen met CP. Een volgens officiële weg vertaalde Nederlandse EDACS versie is gescoord door verschillende logopedisten (één bekend met het kind en één onbekend met het kind). Ouders hebben het EDACS ook geclassificeerd bij hun kind aan de hand van het klinische stroomdiagram in figuur 1.



Figuur 1. klinisch stroomdiagram EDACS.

De gebruiksvriendelijkheid van het EDACS was over het algemeen goed. Er was een goede overeenstemming in classificeren tussen de logopedist die het kind kent en de logopedist voor wie het kind onbekend was (n=31). Ook de 81 ouders bereikten een goede overeenstemming met de classificatie van logopedisten. Er was een significante, positieve correlatie tussen het EDACS en de Dysphagia Management Staging Scale (DMSS). Gebaseerd op deze resultaten kon geconcludeerd worden dat de Nederlandse versie van het EDACS betrouwbaar en valide is en gebruikt kan worden door zowel logopedisten die bekend zijn met het kind als onbekend met het kind. We verwachten dat door het gebruik van het EDACS de bewustwording ten aanzien van veiligheid en efficiëntie van eten en drinken toeneemt

bij de verschillende betrokkenen en dat zorgprofessionals en ouders vaker dezelfde taal zullen spreken.

In **hoofdstuk 5** hebben we de Drooling Quotiënt 10 minuten (DQ10) versie en de Drooling Quotiënt 5 minuten (DQ5) versie onderzocht als objectief meetinstrument voor het evalueren van de ernst van speekselverlies voor en na behandelingen. Er waren geen data bekend over de validiteit en betrouwbaarheid van de DQ10 en vanuit klinisch oogpunt zou het waardevol zijn om de observatie/scoringtijd te reduceren. Uit onderzoek is gebleken dat de DQ10 onderling uitwisselbaar is met de DQ5. Daarmee is de DQ5 dus tijd-, en kostenbesparend, terwijl de validiteit en de interbeoordelaars-, en intrabeoordelaars-betrouwbaarheid behouden blijven. Er wordt een afbreekpunt voorgesteld dat behulpzaam kan zijn voor klinische besluitvorming.

In **hoofdstuk 6** (deel 2) wordt een internationale, op wetenschap gebaseerde benadering gepresenteerd die is voortgekomen uit het zorgpad voor speekselverlies (sialorrhea) van de American Academy for Cerebral Palsy and Developmental Medicine (AACPDM). Een uitgebreid overzicht van zowel het diagnostische als interventieproces voor speekselverlies bij kinderen en jongeren met CP tot de leeftijd van 25 jaar is beschreven. Dit review bevat de gevonden niveaus van evidentie voor het onderzoek en de behandelvormen van speekselverlies wat betreft oraal motorische interventies, gedragstherapie, orale applicaties, farmacologische behandeling, chemodenervatie bij Botuline Toxine en chirurgische interventies. Stroomdiagrammen voor onderzoek en behandeling worden weergegeven.

Hoofdstuk 7 beschrijft de gepersonaliseerde benadering van speekselverlies bij een specifieke groep kinderen met progressieve dystonie (MEGDEL syndroom). De heterogeniteit van de vier gepresenteerde casussen laat zien dat een stapsgewijze en op maat afgestemde benadering noodzakelijk is.

In **hoofdstuk 8** wordt het onderzoek beschreven dat verricht is naar nadelige effecten op de oraal motorische functies ná injecties met Botuline Toxine in de submandibulaire klieren. Dit onderzoek is verricht bij 209 kinderen met hinderlijk speekselverlies. Tijdelijke bijwerkingen traden op in 33% van de 209 behandelingen. Bijna 80% van de bijwerkingen werd als mild beschreven en bijna 9% als ernstig. Ongeveer 54% van de bijwerkingen verdween spontaan binnen 4 weken terwijl 3% persisteerde na 32 weken. Een diagnose CP, een hogere dosis Botuline Toxine en een DQ5 van < 18 in de voormeting, waren de onafhankelijke voorspellers voor bijwerkingen. Het is belangrijk dat vóór het gebruik van Botuline Toxine voor speekselverlies mogelijke bijwerkingen worden besproken. Het is tevens van belang om de oraal motorische functies goed te monitoren want een reeds bestaande dysfagie kan verergeren. De geïdentificeerde klinische voorspellers kunnen behulpzaam zijn bij het verbeteren van de patiëntselectie voor deze behandeling.

In **hoofdstuk 9** worden bij 160 kinderen, die Botuline Toxine in hun submandibulaire klieren kregen in verband met speekselverlies, de veranderingen in objectieve en subjectieve metingen van de speekselernst geëvalueerd. Tevens wordt de wederzijds relatie tussen de metingen onderzocht. Een klinische respons was gedefinieerd als ≥ 50% reductie van de (objectieve) DQ5 en/of een reductie van minimaal een afname van 2 standaard deviaties (SDs) van de (subjectieve) VAS-ernst bij 8 weken na injectie vergeleken met de voormeting. Een oudervragenlijst is gebruikt om de impact van speekselverlies bij responders (kinderen die voldeden aan de responsdefinitie) en bij non-responders te onderzoeken. Resultaten toonden dat er 112 kinderen (70%) responders waren. Hun gemiddelde VAS-ernst en DQ5 sores waren significant lager bij de 32-weekse nameting vergeleken met de baselinemeting. Verschillen in de veranderingen in impact van speekselverlies op de dagelijkse zorg, economische consequenties, de sociale interactie en het zelfbewustzijn zijn weergegeven bij responders en non responders. Het bleek dat een klinisch relevante respons, gebaseerd op een combinatie van objectieve en subjectieve maten van speekselverlies, gepaard ging met positieve veranderingen in de mate van impact.

Hoofdstuk 10 bevat de general discussion waar kritisch wordt terug gekeken op de studies in dit proefschrift en gereflecteerd wordt op de consequenties van deze studies. De studies in dit proefschrift waren bedoeld om de diagnostiek van 'oral motor performance' bij kinderen met neurologische beperkingen te verfijnen en om een gepersonaliseerde benadering van de behandeling van speekselverlies te ontwikkelen. Deze ambitie was gebaseerd op de grote uitdagingen waarmee slik- en speekselcontroleteams worden geconfronteerd tijdens het proces van diagnose en behandeling van dysfagie en speekselverlies. In de afgelopen 20 jaar hebben meer dan 1000 kinderen het academische slik- en speekselcontroleteam van het Radboud universitair medisch centrum bezocht. Deze ervaring, eerder promotieonderzoek en de studies die in dit proefschrift zijn gepresenteerd, hebben geleid tot nieuwe inzichten met betrekking tot de metingen en behandeling van de 'oral motor performance'.

Suggesties voor toekomstig onderzoek:

Ondanks wetenschappelijke ontwikkelingen blijven dysfagie en speekselverlies uiterst uitdagende klinische problemen, vooral bij (jonge) kinderen met neurologische ontwikkelingsproblemen of beperkingen. Vanuit dit perspectief wordt gepleit voor een op mechanismen gebaseerde en tegelijkertijd gepersonaliseerde benadering. Een dergelijke benadering vereist het ontrafelen van de pathofysiologie van dysfagie en speekselverlies in detail. Er is bijvoorbeeld nog steeds weinig inzicht waarom het ene kind met CP kwijlt en het andere kind met precies hetzelfde type CP en dezelfde ernst niet. Nader onderzoek met behulp SSEP (somato sensory evoked potentials) zal ons wellicht helpen om de relatie tussen speekselverlies en orale sensaties te begrijpen.

De klinische bruikbaarheid en nauwkeurigheid van zowel de DRIPS als het EDACS zullen verder moeten verder worden verbeterd.

Daar de Nederlandse speekselreducerende behandeling met Botuline Toxine afwijkt van de wereldwijde benadering is het belangrijk om vergelijkende studies te verrichten. Ook zullen we ons meer moeten gaan richten op de karakteristieken van notoire non-responders om zo te begrijpen welke kinderen wel of niet kunnen profiteren van bepaalde behandelingen.

Dankwoord

'It always seems impossible until it's done' (Nelson Mandela)

Wat is het geweldig om een proefschrift te schrijven met zoveel mensen om je heen die het je gunnen, meewerken en meeleven. Heel bijzonder dat ik de ruimte heb gekregen om het op 'mijn' manier te doen. Iedere keer een stukje verder, nooit opgejaagd maar zelf ook verrast als er weer een artikel afgerond en gepubliceerd was. Prachtig dat ik deze kans heb gekregen en trots dat het gelukt is.
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Collega docenten van de vereniging docenten kinderneurorevalidatie (VDKNR), te weten Drs. Ruud Wong Chung, Drs. Florentine Schepers, Drs. Emmeke Faas, Jan Wielders, Caroline Scheijmans, Sandra de Groot, Harry Crombag, Ingrid van den Tillaar en Ilse Oosterom. Wat ben ik blij met zo'n interdisciplinaire docentengroep om samen na te denken en onderwijs te ontwikkelen voor kinderen met CP. Door jullie, maar zeker ook door mijn oud docenten, Renee Lenaerts-Ernst, Els Geerdink en dr. Pauline Aarts, heb ik geleerd om 'totaal' te kijken naar een probleem en vanuit die totaalblik naar een oplossing. Jullie hebben mij mede aangezet om verder na de denken over deze groep kinderen.

Ook een uiting van dank aan de collega-logopedisten in Nederland die op welke wijze dan ook mee hebben gewerkt aan onze onderzoeken en me hebben geïnspireerd. Onderzoek doe je om de praktijk vooruit te brengen en om de zorg voor het kind met eet-/drink- en slikproblemen te verbeteren. Ik hoop met dit proefschrift een stapje in die richting te hebben gezet.

Zeker een woord van dank voor alle medewerkers binnen het Amalia kinderziekenhuis. Fijn om te voelen dat we allemaal een warm hart hebben voor de complexe groep kinderen en dat we elkaar vinden als het nodig is!

Dat buren van onschatbare waarden zijn blijkt wel weer uit het feit dat buurvrouw Mariëtte van den Berg-Kersten de cover heeft gemaakt van dit boek. Dank voor jullie warme aandacht allemaal.

Naast alle mensen binnen mijn werkveld, gaat mijn dankbaarheid ook uit naar al onze vrienden en familie. Op belangrijke en moeilijke momenten in mijn en ons leven waren en zijn jullie er altijd! Vriendschap betekent voor mij vertrouwen en onvoorwaardelijk er voor elkaar zijn. Samen het leven delen, plezier maken en nadenken over dingen die op ons pad komen. Dit gepaard met lekkere etentjes en borreltjes dan kan vriendschap niet stuk.

Mijn allergrootste dank gaat naar mijn overleden ouders (overleden in 2011 en 2017). Zij zijn het geweest die altijd klaar stonden voor mij en gestimuleerd hebben om na te denken en om nieuwsgierig te blijven. Ik weet dat zij trots zouden zijn en genoten zouden hebben van deze dag.
Lieve pap en mam, dit boek draag ik op aan jullie!

Marc, lieve broer, wij gaan samen verder, de liefde voor elkaar en onze overleden broer Robert blijft ons verbinden. Wat ben ik blij met zo'n vrolijke, hardwerkende broer met zo'n groot hart. Ik houd van de wijze waarop jij iedereen omarmt.

Mw. A. van Hooft, lieve Annie, dank voor je liefde en belangstelling voor ons.

Wat is het mooi om dit proces te volbrengen als je kinderen al ouder zijn en begrijpen wat het is om ambities te hebben. Ieder op hun eigen wijze hebben zij mij gesteund en gestimuleerd.

Lieve Michiel, fantastisch zoals jij in het leven staat en samen met Felicia en kleine Axel geniet. Ik bewonder je talent om naar mensen te kijken, je analytische vermogen en je snelle denken. Dank je wel voor het maken van Visio stroomdiagrammen, jij was het die mijn 'simpele' diagrammen omzette in flowcharts zoals het hoorde. Daarbij bleek ook je belangstelling voor mijn vakgebied en konden we echt samen nadenken over de logistiek van interventies. Mooi om deze dag te laten samenvallen met jouw 31e verjaardag; proficiat!

Lieve Francesca, wat heb ik je zien groeien als persoonlijkheid. Ik zie je steeds meer stappen zetten in het nemen van verantwoordelijkheid en dat past je. Ik bewonder de wijze waarop jij, zonder oordeel, klaarstaat voor iedereen. Met je creatieve geest kun je alles of het nu gaat om bakken of meubels maken, bloemschikken of schilderen. Een rijkdom om zoveel talenten te hebben! Ik zie René en jou altijd hard werken! Fijn dat jij deel uit maakt van ons gezin.

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Lieve Rosanne, de jongste, mijn paranimf vandaag. Ik heb je niet zomaar gevraagd om deze rol op je te nemen. Jij was het die jarenlang in de vakanties de “droolingdatabase” heeft ingevuld. Dat deed je zorgvuldig en met belangstelling voor mijn vakgebied. Precies zoals je bent: liefdevol, nadenkend, hulpvaardig, spontaan en geïnteresseerd. Ik herken veel in je en samen delen we de liefde voor de zorg. Mooi dat we in 2019 eerst jouw bruiloft met Wout konden vieren en nu weer een feestje. Ik ben zo trots dat je naast me staat vandaag!

Als laatste een woord van grote dank voor mijn lieve Peter. Zonder jou was dit proefschrift er nooit gekomen. Jij was het die mij stimuleerde om niet naast je op de bank te komen zitten toen onze toekomst er anders uit ging zien dan we misschien hadden bedacht. Jij was het die altijd in mij geloofde en de lekkerste maaltijden voor me neerzette na hard werken. Van ‘buitenaf’ keek je mee en kon ik altijd even reflecteren waarbij jij met je overview en mensenkennis zinvolle commentaren gaf. Ik bewonder je positieve instelling en je doorzettingsvermogen. Ondanks alles hebben we een rijk leven; samen hebben we het goed!

Curriculum vitae

Karen van Hulst was born in Oss, the Netherlands, on December 5th, 1962. She graduated from secondary school (VWO, Titus Brandsma Lyceum in Oss) in 1981 and, thereafter, started her bachelor training in Speech and Language Therapy at the Hogeschool Arnhem-Nijmegen (HAN) in Nijmegen. Since 1985 she has worked as a speech language therapist in a pediatric SLT team, first at the department of Pediatric Neurology and since 2011 at the department of Rehabilitation of the Radboud university medical center, Amalia Children's Hospital, in Nijmegen. The pediatric SLT team is involved in research and diagnostic assessment and treatment of infants and children with complex oral motor disorders and speech and language disorders. Based on scientific research the team has developed several disease specific assessment and treatment trajectories for children with neurologic disorders and syndromes. The team is working for children all over the country and combines patient care with scientific research, that resulted in several studies and publications.

Karen is a member of the swallowing and saliva-control team of the Radboudumc also a member and is specialized in dysphagia and drooling in children with neurodevelopmental disabilities. The swallowing and saliva controle team integrates pediatric neurology, radiology, otorhinolaryngology and rehabilitation and collaborates with the pediatric rehabilitation department of the Sint Maartenskliniek, Nijmegen. Since 2000 she has been involved in several PhD projects of the saliva control team members.

Karen obtained her Master of Science (MSc) in Evidence-Based Practice in 2010 at the University of Amsterdam (2008-2010). In 2012 she started her PhD training in combination with clinical work. In parallel, she has contributed to the development of a national evidence-based guideline for the diagnosis and treatment of children with spasticity (under the leadership of the Dutch Institute for Health Improvement, 2006, revision 2015) and to the development of the national diet-treatment guideline for people with cerebral palsy (2018).

In addition, Karen is lecturing and runs courses for healthcare professionals in pediatric rehabilitation in the Netherlands via the Vereniging Docenten Kinderneurorevalidatie (VDKNR), organized in collaboration with the Radboud Health Academy. She is also a member of the board of the Dutch Academy of Childhood Disability. During her PhD, Karen presented her work at several (inter)national conferences. After her PhD defense, Karen will continue to combine her clinical work with scientific research in her inspiring and enthusiastic SLT team.

PhD Portfolio

Courses

Courses and workshops	Year	ECTS
Master of science EBP, University of Amsterdam	2010	95
Donders introduction course, Radboud university medical center	2015	0.6
Academic writing, Radboud university medical center	2015	3
Writing week, department of Rehabilitation, Radboud university medical center	2017 and 2018	4
TOTAL		**102.6**

Lectures and conferences (part of them)

	Year	ECTS
Proof of teaching at the HAN	2011-2018	40
Prelogopedie symposia Nijmegen (organization and speaker)	2011-2015	6
International Cerebral Palsy Conference (speaker)	2012	1
American Academy Cerebral Palsy Developmental Medicine (AACPDM) Milwaukee (speaker mini symposium)	2013	1
Dutch-ACD, Learn to move symposium (speaker workshop)	2014	1
EMG platform (speaker)	2014	0.3
NVAVG teaching course (speaker)	2015	0.5
Gruppo Italiano de Studio della Disfagia (GISD) (speaker)	2015	1
European Society for Swallowing Disorders (ESSD) (speaker)	2014, 2015, 2016, 2018	4
European Academy Childhood Disabilities (speaker and poster presentations)	2014, 2015, 2017, 2019	8
Vlaamse Vereniging voor Logopedie, Brussel (speaker)	2017	0.5
Symposium Samen Eten, Samen sterk, Rotterdam (speaker)	2017	0.5
Tutor at the pediatric Neurorehabilitation Course the Netherlands	2012-2018	40
TOTAL		**103.8**

Data management form

General information about the data collection

This research project involves human subject data. Oral or written informed consent for collecting such data was obtained from the participants and/or from their parents (or legal representatives) for those younger than 18 years old. All studies have been reviewed by the ethics committee on the basis of the Dutch Code of conduct for health research, the Dutch Code of conduct for responsible use, the Dutch Personal Data Protection Act, and the Medical Treatment Agreement Act.

FAIR principles

Findable:

New data were collected and stored in a secure "drooling" database (named DROOLING_TBL_2007.MDB), on a protected server at the department of Rehabilitation of the Radboud university medical center. The datasets are named: DB_DRIPS, DB_EDACS, DB_DQ5, DB_NEGEFFBoNT and DB_CHANGEIMPACT. Documentation (i.e. read me file) to describe the datasets is provided on the department server. At the end of 2019, the ACCESS database Drooling.version 2.0.9. will be converted to CASTOR.

Accessible:

Only members of the research group have access to the database. Paper records are stored in the department's archive. It is not yet possible to make the data available in a public repository. However, all data will be available on request by contacting the staff secretary of the department of Rehabilitation of the Radboud university medical center (secretariaatstaf.reval@radboudumc.nl).

Interpretable:

Documentation has been added to the datasets to make them interpretable. The documentation contains links to publications, references to the location of the datasets, and a description of the datasets. The data are stored in SPSS format. No existing data standards have been used such as vocabularies, ontology's or thesauri.

Reusable:

The data will be stored for at least 10 years and can therefore also be reused in this time period. There is no embargo on the accessibility of the data.

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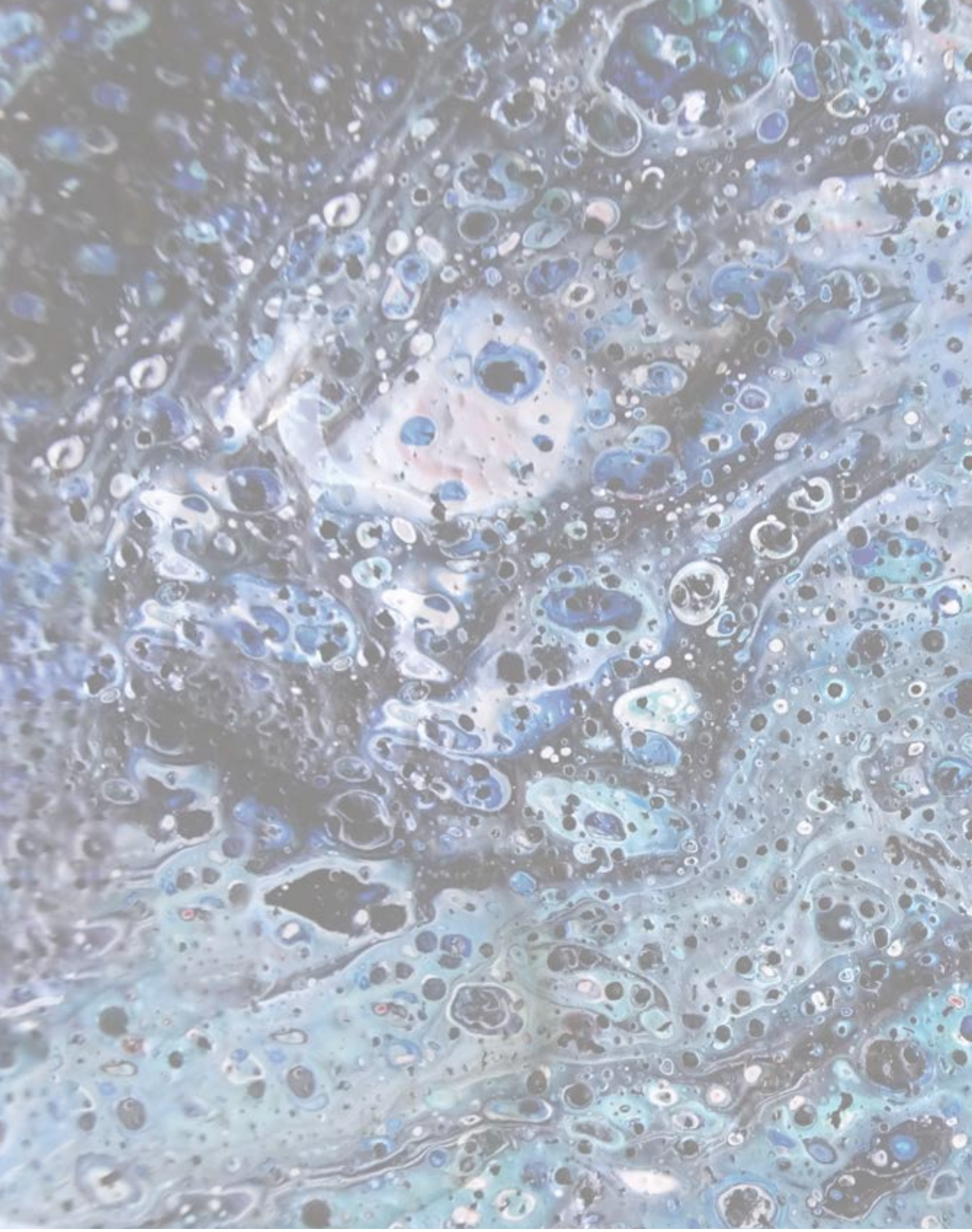

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