Exploring Novel Treatments for Drooling in Neurological Disorders

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Abstract

Both in clinical and experimental contexts, the treatment of drooling, or sialorrhea, in children with neurological disorders (ND) is still a challenge. In literature, *Drooling Impact Scale* (DIS), *modified Teachers' Drooling Scale* (mTDS), and *Drooling Severity and Frequency Scale* (DSFS) are subjective methods of measurement in sialorrhea. The purpose of this study is to investigate their accuracy in the assessment of severity, frequency, complications of drooling and objective evaluation of treatment effectiveness and safety. 31 children (10 females and 21 males; age range 1y-17y, average 7y 3mo, median 6y, S.D. 4y 5mo) with drooling and an ND (10 with an acquired ND, 19 with a congenital ND, 2 with a muscular disorder) were included. Each patient was evaluated with the three scales and each score obtained was compared to the others through the Pearson r index. Results showed a significant correlation among them (DSFS-DIS r=0.86; DSFS-mTDS r=0.88; DIS-mTDS r=0.87). Moreover, mTDS and DSFS scores were compared to five domains included in the DIS. Results showed a strong significant correlation with the items: *Severity* (r=0.87,0.93), *Level of care* (r=0.84,0.82), and *Impact on family life* (r=0.77,0.75). The items *Complications* (r=0.53,0.60) and *Impact on the child's life* (r=0.48,0.46) showed a significant correlation too. In each of the DIS domains, the Mann-Whitney test confirmed significant differences (p<0.005) between patients with mild drooling (DSFS 2-5) and those with moderate-to-severe drooling (DSFS 6-9). In conclusion, DSFS and mTDS are accurate in evaluating the severity and frequency of drooling. The DIS scale accurately assesses the physical complications of the anterior drooling and contains general questions about the psychological burden, but it doesn't include the evaluation of the posterior drooling and the treatment effectiveness. We recommend the introduction of a representative scale for the direct assignment of the DIS score by the child itself.

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Nomenclature

Acronyms / Abbreviations

p	*p value*
r	*Pearson correlation coefficient*
AA	*Atypical Absence*
AE	*Acute Encephalopathy*
AEDs	*Anti-Epileptic Drugs*
AS	*angelman Syndrome*
ASD	*Autism Spectrum Disorder*
CDKL5	*Cyclin-Dependent Kinase-Like 5 Syndrome*
CG	*Crouching Gait*
CI	*Confidence Interval*
CN	*Cranial Nerve*
CNS	*Central Nervous System*
CP	*Cerebral Palsy*
CPG	*Central Pattern Generator*
CPS	*Complex Partial Seizures*
d	*day(s)*
DD	*Developmental Delay*

DIS *Drooling Impact Scale*

DIS-d1/5 *Drooling Impact Scale-domain1/5*

DIS-tot *Drooling Impact Scale-total*

DQ *Drooling Quotient*

DS *Dravet Syndrome*

DSFS *Drooling Severity and Frequency Scale*

e.g. *exempli gratia, for example*

EEG *ElectroEncephalography*

et al. *et alia, and others*

FISH *Fluorescence In Situ Hybridization*

FOXG1 *Forkhead bOX protein G1*

FS *Febrile Seizures*

FSz *complex Febrile Seizures*

GCS *Generalized Clonic Seizures*

GEFS+ *Generalized Epilepsy with Febrile Seizures plus*

GERD *Gastro-Esophageal Reflux Disease*

GM-CSF *Granulocyte-Macrophage Colony-Stimulating Factor*

GMFCS *Gross Motor Function Classification System*

GMS *Generalized Motor Seizures*

GTCS *Generalized Tonic-Clonic Seizures*

h *hour(s)*

HFM *HemiFacial Macrosomia*

HRQOL *Health-Related Quality Of Life*

HS *Hyperthermia Sensitivity*

i.e. *id est, for example*

IC *Imprinting Center*

ID *Intellectual Disability*

Ig *ImmunoGlobulin*

IL *Interleukin*

IPS *Intermittent Photic Stimulation*

IUGR *Intrauterine Growth Retardation*

LGS *Lennox-Gastaut Syndrome*

max *maximum*

MBD *Methyl Binding Domain*

mBMRS *modified Behavioral and Medical Rating Scale*

MECP2 *Methyl CpG binding Protein 2*

MEF2C *Myocite-specific Enhancer Factor 2C*

min *minimum*

mo *month(s)*

MSz *Myoclonic Seizures*

mTDS *modified Teachers' Drooling Scale*

n. *number*

ND *Neurological Disorder*

NLS *Nuclear Localization Signal*

NRS *Numerical Rating Scale*

NTS *Nucleus Tractus Solitarius*

OAVS *Oculo-Auriculo-Vertebral Syndrome*

OFC *Occipito-Frontal Circumference*

OMIM *Online Mendelian Inheritance in Man*

OS *Obtundation Status*

PD *Parkinson Disease*

q.4-6h *quaque 3 hora, every 4-6 hours*

q.d. *quaque die, every day*

q.h.s. *quaque hora somni, every bed time*

REM *Rapid Eye Movement*

RFLP *Restriction Fragment Lenght Polymorphism*

RTT, RS *Rett Syndrome*

S.D. *Standard Deviation*

S.L. *SubLingually*

SE *Sudden dEath*

SE *convulsive Status Epilepticus*

SM *SubMandibular*

SMEI *Severe Myoclonic Epilepsy of Infancy*

SNAP-25 *Synaptosome Associated Protein-25*

SUDEP *Sudden Unexpected Death in EPilepsy Syndrome*

SWs *Spike Waves*

t.i.d. *three times a day*

TCF4 *TransCription Factor 4*

TNF *Tumor Necrosis Factor*

TRD *Transcriptional Repression Domain*

U *Mann-Whitney test*

UBE3A *UBiquitin-protein ligase E3A*

UES *Upper Esophageal Sphincter*

UPD *UniParental Disomy*

US *UltraSound*

VAS *Visual Analogue Scale*

VEGF *Vascular Endothelial Growth Factor*

vs. *versus*

w *week(s)*

XDML *X-linked Dominant Male Lethal*

y *year(s)*

Chapter 1

Drooling and Neurological Disorders

1.1 Introduction

One of the most complex aspects of the neurological patient consists of the wide variety of his clinical presentations. The first approach is aimed at recognizing the diagnostic neurological signs of the pathology. However, to obtain adequate patient management, it is always necessary to evaluate the patient as a whole, and also analyze any associated conditions. The patient's quality of life is often influenced by these associated conditions and sialorrhea is an example. In taking charge of a neurological patient who presents with sialorrhea, drooling recognition and therapeutic management represent a fundamental step for the care of the patient and his family.

1.1.1 Drooling definition

Drooling (sialorrhea or excessive salivation) is defined as saliva beyond the margin of the lip [18]. Generally, it is considered as a physiological condition in infants before 18 months of age and a pathological one in patients after four years of age. Sialorrhea is very common in patients with neurological disorders, such as neurologically impaired children, adults affected by Parkinson's disease, or who have suffered a cerebrovascular accident. Facial oral-motor control is the most important factor involved in drooling physiopathology. Alternative causes include hypersalivation and combinations of other clinical conditions (i.e. dental malocclusion and postural problems) [18].

1.1.2 Drooling clinical, social, and family implications

Children's and their caregivers' quality of life can be seriously compromised by persistent drooling, which can lead to several related conditions, some of them are described in Tab. 1.1 [22].

The effects of drooling
Chronically irritated, chapped or macerated facial skin
Increased perioral infections
A foul-smelling odour
Dehydration due to chronic fluid and nutrient loss
A chilling feeling in cold weather conditions

Table 1.1 Some examples of drooling consequences in children's health and quality of life.

Drooling impact on patients' quality of life depends on the type of sialorrhea, its severity, frequency, and many other key features, which must be evaluated by the clinicians during the examination. At first, from a clinical point of view, sialorrhea can be classified as anterior and posterior; both can occur separately or simultaneously and lead to different clinical consequences.

Anterior sialorrhea is the unintentional loss of saliva from the mouth to the margin of the lip [10]. It can lead to both psychosocial and physical health problems. Social isolation is a frequent consequence of children with severe drooling. Their excessive salivation may be responsible for social rejection by their peers and sometimes by their caregivers, because of the unpleasant odor. Clothes have to be changed frequently and saliva can damage objects, such as toys, books, and computers. These consequences may also affect the social and cultural education of the patient, who may be perceived negatively by the social group and his intellectual capacity can be underestimated. In addition to the socio-cultural impact, the physical effects of drooling (as reported in Fig. 1.1) affect the quality of life of the patients and that of their families or caregivers [10].

Shih-Chung Chang et al. [7] in "The association of drooling and health-related quality of life in children with cerebral palsy" investigated the association between drooling in children with cerebral palsy (CP) and their health-related quality of life (HRQOL), as well as the possible variables that predict their HRQOL. This study showed that the physical health summary scores and psychosocial health summary scores were significantly lower in the

children with CP that drooled than in the children with CP that did not drool. These results were compatible with previous studies showing that drooling may lead to health-related problems such as skin maceration, recurrent pneumonia, and malnutrition. Although their result showed a significant level of correlation between drooling and psychosocial HRQOL, the correlation coefficient showed only a lower level of correlation. The more severe the drooling was (without considering the type of CP), the lower the physical and psychosocial health quality of life was in the children with CP. The gross motor development level and ranking of drooling predicted the physical health score better, and the language development level predicted the psychosocial health score better. About concerning providing early intervention programs for children with CP, their developmental status should be assessed as well as their drooling problem, which has a negative correlation on their HRQOL [7].

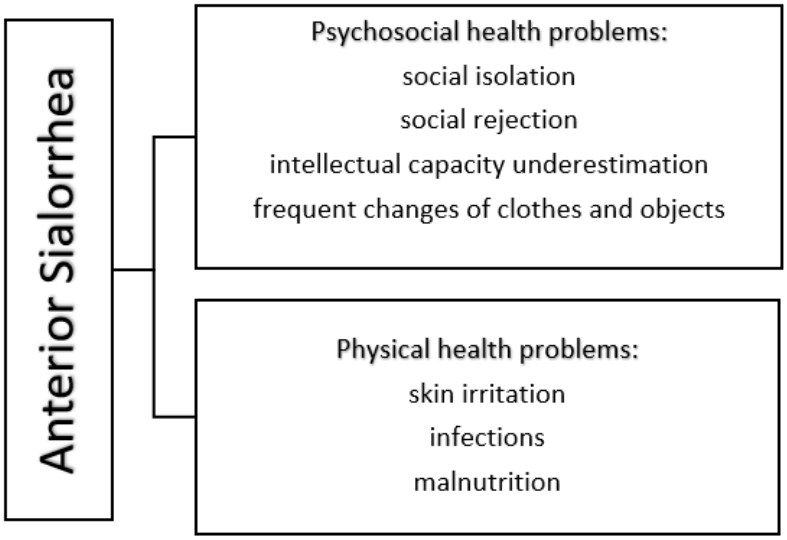


Fig. 1.1 Physical and psychosocial impacts of anterior sialorrhea.

Posterior sialorrhea is the flowing of saliva from the tongue to the pharynx [10]. It is common in children with severe dysphagia, especially with a severe pharyngeal phase impairment. The major risk of these patients is the aspiration of saliva into the tracheobronchial tree, which can lead to recurrent pneumonia [10]. This type of pneumonia can lead to respiratory problems, which may be treated through a reduction of saliva aspiration. Park et al. [23] tried to use botulinum toxin injections and demonstrated a successful reduction in saliva aspiration, using a radionuclide assessment known as a salivagram [23]. Another invasive method is represented by surgical intervention. Vijayasekaran et al. [29] studied a group of 62 children submitted to surgical treatment for sialorrhea, and showed an increase in the

mean oxygen saturation and reduction in the frequency of pneumonia. Thus, therapeutic interventions can effectively improve respiratory health in these patients [29].

Fig. 1.2 The effects of posterior sialorrhea.

1.2 Physiopathology

The pathophysiology of drooling is still poorly understood, but it represents a fundamental aspect to study its causes and treatment. In the following paragraphs, we will try to describe simply and effectively the physiological aspects of salivation, to then understand the pathophysiological alterations responsible for hypersalivation and/or drooling.

1.2.1 Physiology of salivation

In this section, we will deal with saliva, and its physiological functions, composition, and production. These aspects are interrelated and work together to maintain salivation homeostasis. It is therefore easy to understand that an alteration of any of these aspects can be responsible not only for sialorrhea but also for its clinical consequences. The chemical-physical composition of saliva is for example the main determinant of its odor, which, if bad, can cause serious embarrassment in the patient affected by drooling. The same applies to the excessive production of saliva itself, which can be a contributing cause, albeit rare, to the onset of drooling. The intent of these paragraphs is therefore to make the reader understand the physiological functioning of salivation, to then study its pathological alterations.

Physiology of saliva production

Saliva is a mucoserous exocrine secretion from major and minor salivary glands. The major salivary glands include the paired parotid glands, which are located opposite the maxillary first molars, and the submandibular and sublingual glands, which are found on the floor of the mouth. Minor glands that produce saliva are found in the lower lip, tongue, palate, cheeks, and pharynx [20]. The terms *major* and *minor* do not refer to the clinical importance of the

glands, but their anatomic size and the quantity of saliva produced. Major glands produce more saliva than minor glands, but the quality of contents varies. Minor glands are the most important because of their protective components.

The average daily flow of the whole saliva varies between 1 and 1.5 L. Percentage contributions of the different salivary glands during unstimulated flow are as follows: 20% from the parotid, 65% from submandibular, 7% to 8% from sublingual, and less than 10% from numerous minor glands. In the stimulated high flow rates, the parotid contributes more than 50% of total salivary secretions [20].

Salivary glands have different types of secretion, classified as serous, mucous, or mixed. Whole saliva is a complex mix of these fluids. The parotid glands have a serous secretion, the sublingual and submandibular glands a mixed secretion, whereas mucous secretions derived from the minor glands. Microscopically, salivary glands are composed of three types of cells: acinar cells, various duct system cells, and myoepithelial cells. Saliva is first secreted in acinar cells, which determine the type of secretion. Duct system cells found in the salivary ducts are classified as intercalated, striated, and excretory. Intercalated duct cells are the first duct network connecting acinar secretions to the rest of the gland. These cells are not involved in the modification of electrolytes, as are the remaining duct cells. Striated cells are second in the network, functioning as electrolyte regulation in resorbing sodium. The final duct cells, the excretory duct cells, contribute by continuing sodium resorption and secreting potassium. Excretory duct cells are the last part of the duct network before saliva reaches the oral cavity. Myoepithelial cells, which are long cell processes wrapped around acinar cells, contract on stimulation to constrict the acinar. This function of secreting or "squeezing out" and accumulating fluid, is the result of a purely neural process [20].

Salivary flow rates have a great variability and are first determined by the functional state of the salivary glands. In the steady-state, the accepted range of normal flow is anything above 0.1 mL/min. This value increases to 0.2 mL/min when salivation is stimulated. Any unstimulated flow rate below 0.1 mL/min is considered hypofunction. However, these numbers may consistently vary among individuals and salivary flow is a very individualized measurement [20]. Total daily flow of whole saliva measures, on average, between 500 mL and 1.5 L. Circadian (daily) low flow occurs during sleep, circannual (yearly) low flow occurs during summer, whereas peak flow is during winter. Circadian flow variations affect not only flow but also the concentration level of salivary components such as salivary electrolytes and proteins [20]. The different areas of the mouth produce a different quantity of saliva

every day and regional variation in intraoral flow is site-specific. The mandibular lingual is a site of high volume (referred to as *"salivary highways"*), whereas the maxillary anterior and interproximal are sites of low volume flow (referred to as *"salivary byways"*). In the area of *salivary byways*, acid produced by bacteria remains in longer contact with oral structures, because of the low salivary flow rate. The regional clearance rate is more successful in the *salivary highways* region, where salivary flow provides a wide antibacterial protection [20]. This variability in intraorally protection provided by saliva is also determined by the different composition of the secretions of different salivary glands. For example, parotid saliva contains amylase, proline-rich proteins, and agglutinins with minute amounts of cystatins, lysozymes, and extra parotid glycoproteins. As a result, maxillary premolars exhibit higher counts of salivary agglutinins due to the proximity of the parotid duct. Sublingual saliva contributes high concentrations of both types of mucins, MG1 and MG2, as well as high levels of lysozymes. Submandibular saliva contains the largest amount of cystatins, whereas palatine secretions offer MG1 mucins and relatively high amylase concentrations [20].

The salivary center is located in the medulla and its activation is triggered by three principal types of stimuli: *mechanical* (the act of chewing), *gustatory* (with acid the most stimulating trigger and sweet the least stimulating), and *olfactory* (a surprisingly poor stimulus). Many factors influence saliva production, including psychic conditions, pain, medication, and local or systemic diseases [20]. Salivary secretion is primarily controlled by the autonomic nervous system, both sympathetic and parasympathetic nerve fibers innervate salivary glands. Parasympathetic preganglionic fibers that arise from the superior salivatory nucleus emerge from the brainstem and travel with the facial nerve into its vertical position in the mastoid, where they subsequently separate to run across the middle ear as the chorda tympani nerve. After exiting from the middle ear, the chorda tympani nerve joins the lingual nerve. The preganglionic fibers then synapse in the submandibular ganglion, where postganglionic fibers leave to innervate the submandibular and sublingual glands. Parasympathetic preganglionic fibers arising from the inferior salivatory nucleus leave the brainstem with the glossopharyngeal nerve. The fibers then leave the glossopharyngeal nerve to ascend in the middle ear as the Jacobson's nerve. The fibers then join sympathetic nerves from the carotid system to form the tympanic plexus. The fibers of the plexus leave the middle ear as the lesser superficial petrosal nerve and synapse in the otic ganglion. Postganglionic fibers then follow the auriculotemporal nerve to the parotid glands [24]. Sympathetic fibers arise in the upper thoracic segments of the spinal cord and synapse in the superior cervical ganglion. Postganglionic fibers leave the superior cervical ganglion and innervate the acini, ducts, and blood vessels [24]. Parasympathetic stimulation of the salivary glands results in increased

salivation, because of the increased activity of acinar and ductal cells. The sympathetic nervous system influences the blood flow to the salivary glands and activates myoepithelial cells with resulting expulsion of saliva from the glands [24]. These two autonomic nervous systems are regulated by different receptors and neurotransmitters. However, it has been demonstrated that the activation of one receptor (i.e. parasympathetic one) often enhances and complements another receptor (i.e. sympathetic one), which emphasizes the hypothesis that salivary secretion is controlled by both parasympathetic and sympathetic nervous system and their roles usually are interchangeable. The two systems cooperate to maintain salivary homeostasis [20].

The components of saliva

Saliva is a clear, slightly acid fluid, composed of more than 99% water. It is produced as an isotonic fluid in the acinar cells, but it becomes hypotonic as it travels through the duct network. Saliva hypotonicity is necessary to maintain a correct sense of taste, without the influence of the plasma sodium level. The main components of saliva are electrolytes (sodium, potassium, calcium, magnesium, bicarbonate, and phosphates), proteins (immunoglobulins and enzymes), mucins, and nitrogenous products (urea and ammonia). Each component plays its role and is multifunctional (performing more than one function), redundant (performing similar functions but to different extents), and amphifunctional (acting both for and against the host) [20]. The normal pH of saliva is 6 to 7 and it is modulated by the combination of bicarbonates, phosphates, and urea. Macromolecule proteins and mucins serve to protect from microorganisms and contribute to dental plaque metabolism. antibacterial action is provided by immunoglobulins and enzymes. Calcium, phosphate, and proteins work together to modulate demineralization and remineralization [20].

The functions of saliva

Salivary functions can be organized into 5 major categories that serve to maintain oral health and create an appropriate ecologic balance: (1) lubrication and protection, (2) buffering action and clearance, (3) maintenance of tooth integrity, (4) antibacterial activity, and (5) taste and digestion. As stated earlier, salivary components work in concert in overlapping, multifunctioning roles, which can be simultaneously beneficial and detrimental.

Functions of saliva
Lubrication and protection
Buffering action and clearance
Maintenance of tooth integrity
Antibacterial activity
Taste and digestion

Table 1.2 The five major functions of saliva.

Lubrification and protection Many types of irritants can attack and damage oral tissues, such as proteolytic and hydrolytic enzymes produced by bacteria, carcinogens from smoking and pollution, and exogenous chemicals. The components of saliva work together to lubricate and protect oral mucosa, but the mucins play the central role. Mucins are complex protein molecules that form a stick barrier against irritants, thanks to their high viscosity, high elasticity, and strong adhesiveness. They are secreted by the major salivary glands, particularly, by sublingual and submandibular glands, which produce MG1 (a high-molecular-weight, highly glycosylated mucin) and MG2 (a low-molecular-weight, single-glycosylated peptide chain mucin). MG1 and MG2 are responsible for lubrification, aided by mastication, speech and swallowing, and also antibacterial activity, modulating the adhesion of microorganism to oral tissues surfaces [20].

Buffering action and clearance The second function of saliva is modulating oral pH and bacterial proliferation. Oral pH is composed of the pH of saliva and especially the pH of plaque. The plaque characteristics are fundamental to control bacterial activities and to maintain a buffering action on caries. Many factors may influence plaque homeostasis. At first, the pH of saliva contributes to neutralizing acids on the tooth surface. The pH of the plaque is related to food intake: at rest (2 to 2.5 hours after the last intake of exogenous carbohydrates) is 6 to 7. The pH rises during the first 5 minutes after the intake of most foods and then falls to its lowest level, to 6.1 or lower, approximately 15 minutes after food consumption. Unless there is additional ingestion of fermentable carbohydrates, the pH of plaque gradually returns to its resting pH of 6 to 7 [20]. Another influencing factor of intraoral pH is the salivary flow rate and its modification. A mechanical stimulus, such as chewing and the muscular activity of the lips and tongue, can augment salivary flow and oral clearance. Moreover, chewing products contain no fermentable carbohydrates, which can aid in the modulation of plaque pH. The best neutralizing action is performed by some components of saliva: bicarbonate, phosphate, urea, and proteins. Bicarbonate is the most

important system of neutralization of acids, aided by ammonia. Ammonia is released by the metabolism of urea and histidine-rich proteins, which represent more than 90% of the nonbicarbonate buffering ability of saliva [20].

Maintainance of tooth integrity Facilitating the demineralization and remineralization process represents the third function of saliva. Demineralization consists of the dissolution of the crystal pellicle, which protects the teeth surface. It is activated by acids diffused through the plaque at a pH of 5-5.5, which is the critical pH range for the development of caries. The key function of saliva is buffering and neutralizing the acidity of plaque pH, to prevent caries formation and progression. Remineralization is the process of replacing lost minerals through the organic matrix of the enamel to the crystals [20]. Salivary proteins maintain high concentrations of calcium and phosphate, which provide maturation and remineralization of enamel [20].

Antibacterial activity The fourth function of saliva is protecting teeth and mucosal surfaces from microorganisms. Antibacterial activity is performed by different components of saliva, including immunological and non-immunological factors. The largest immunological component of saliva is immunoglobulins, particularly IgA, IgG, and IgM. IgA is the mucosal immunoglobulin, produced by plasma cells in connective tissues and translocated through the duct cells of major and minor salivary glands. It acts to neutralize the virus and bacterial antigens, whereas it is not able to activate complement. Other immunoglobulins are in low quantities and probably come from the gingival crevicular fluid. The immunological components of saliva cooperate to maintain the great balance between immunological activation against host pathogens and immunological tolerance to self-antigens and food antigens. The fluid secreted by salivary glands contains several non-immunological agents, such as proteins, mucins, peptides, and enzymes (lactoferrin, lysozyme, and peroxidase). They work together with immunoglobulins to provide and maintain oral health and safety against microorganism invasion. Mucins, especially MG2, bind mucosal pathogens in complex with IgA. Lactoferrin exhibits two different antimicrobial effects. The first effect is called *"nutritional immunity"* and consists of the lactoferrin capacity of binding iron, an essential element for cariogenic streptococci. The sensitivity of Streptococcus mutans represents the second antibacterial effect of lactoferrin. The parotid glands produce lysozymes, derived from the basal cells of striated ducts. Lysozyme splits bacterial cell walls and promotes the clearance of bacteria through aggregation. Acinar cells secrete peroxidase, also known as sialoperoxidase or lactoperoxidase, an enzyme that neutralizes the oxidizing effect of hydrogen peroxide. Cystatins, a family of cysteine-containing proteins, inhibit cysteine-proteinase involved in the

pathogenesis of periodontal diseases. Finally, glycoproteins, statherins, agglutinins, histidine-rich proteins, and proline-rich proteins provide the agglutination pf bacterial cells and protect oral mucosa from bacterial adhesion and colonization. Salivary protein concentration varies among individuals and depends on the flow rate (they are directly proportional), and other additional factors, such as stress, inflammation, infection, and hormonal changes [20].

Taste and digestion Tasting capacity of salty and nutrient sources is enhanced by the hypotonicity of saliva. The final function of saliva is beginning the digestive process, using the activity of amylase. Salivary amylase is a digestive enzyme secreted by the parotid gland, which catalyzes the initial phase of starch and fat catabolism. The most of starch digestion, however, happens in duodenum lumen, resulting from pancreatic amylase. More importantly, saliva serves to lubricate the food bolus, which aids in swallowing [20].

1.2.2 Neurophysiology of swallowing

Swallowing is a complex process that allows for the oral contents to pass from the mouth into the esophagus and can be divided into three phases (*oral*, *pharingeal*, and *exophageal*). Its functionality depends on the coordinated activity of several muscles, which alternate contraction and inhibition of their fibers. The musculature of mouth, tongue, larynx, pharynx, and esophagus is completely involved. The complexity of this contraction system is regulated by a fine neurological control, which includes different structures, from the cerebral cortex to the medulla oblongata. Each phase of swallowing has a different innervation, which influences the main characteristics of the phase itself: the oral phase is often accepted as voluntary, while the pharyngeal phase is considered a reflex response, and the esophageal phase is mainly under the dual control of the somatic and autonomic nervous systems [12]. The oropharyngeal phase lasts 0.6-1.0 s and is very complex, whereas the esophageal phase is slower and simpler. It consists of a peristaltic contraction of esophageal muscles that lasts more than 10 s [12].

Oral phase of swallowing

During the oral phase of swallowing the tongue presses the bolus against the hard palate and then toward the oropharynx. This phase and its neurological control have been studied in animal models. In humans, the initial process of swallowing is more complex and involves several nervous structures, even above the brain stem. The oral phase is voluntary and its duration depends on taste, environment, hunger, motivation, and consciousness for the human subject [12]. At first, swallowing stimulation can be divided into two types: voluntarily

induced swallowing and reflexively induced one. The voluntary swallowing is activated by the passage of bolus through the oral mucosa, whereas the reflexive process appears between meals and during non-REM sleep, triggered by the amount of saliva accumulated in the mouth. The identification of oral contents (i.e. saliva, or bolus) is provided by the sensory inputs deriving from mechanoreceptors, chemoreceptors, and thermoreceptors in the oral cavity, tongue, and pharynx (IX and X CN). These triggers are sufficient for the spontaneous swallowing stimulation, whereas the initiation of the voluntarily swallowing requires a cortical drive. The cerebral cortex modulates the reflexively swallowing, communicating with subcortical structures. Other factors influencing the oral phase of swallowing are the bolus size and type, and the site of sensory inputs. Different research studies have reported the differences between water and solid food ingestion in swallowing stimulation. A swallow is not induced by water infusion into the valleculae until the liquid reached the pyriform sinuses and aryepiglottic folds. A swallow, however, may be initiated earlier when the bolus makes contact with the upper third of the epiglottis than when it is confined to the valleculae and pyriform sinuses at the pharynx. In normal human subjects, it is evident that there is usually a gradual accumulation of prepared food on the posterior surface of the tongue, and this solid food reaches the valleculae in advance of the initiation of the swallow [12]. The size of the bolus does not alter the sequence of events during oropharyngeal swallowing but modulates the timing of each part of the swallow. The oral and pharyngeal stages occur in a rapid sequence when the volume of the swallow is small (1-2 mL), whereas with a large bolus size (2-20 mL) this time increases. This phenomenon is called *"piecemeal deglutition"* [12]. Once swallowing is initiated, the cascade of the sequential muscle activation does not essentially alter from the perioral muscles downward [12]. The first acting muscles are the suprahyoid muscles, which elevate the tongue, and the lips and cheek muscles (i.e. orbicularis oris and buccinator muscles), which prevent the escape of solid or liquid from the oral cavity (VII CN).

The initiation of swallowing is induced by peripheral stimuli that run within the maxillary branch of the trigeminal nerve, the glossopharyngeal nerve, and the vagus nerve, especially its superior laryngeal branch. These nerves innervate the dorsum of the tongue, the epiglottis, the pillar of the fauces, and the walls of the pharynx [12]. All the afferent fibers converge at the brain stem, in the nucleus tractus solitarius (NTS). The swallowing process is also governed by the cerebral cortex: NTS receives peripheral sensory inputs and cortical descending inputs. Some sensory inputs that initiate swallowing are transmitted to the region of the cortex that facilitates the initiation of the swallowing. The cerebral cortex probably controls

the swallowing process by decreasing the threshold to evoke swallowing during repeated swallowing [12].

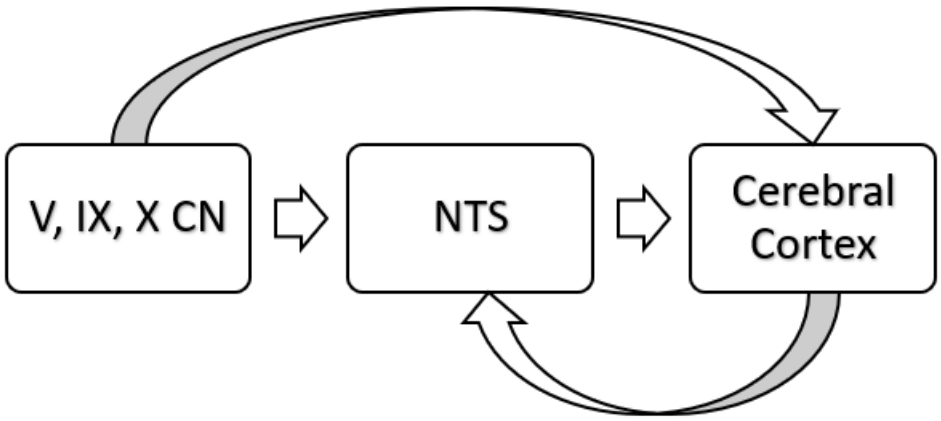


Fig. 1.3 The nervous structures involved in the oral phase of swallowing. CN, cranial nerves; NTS, nucleus tractus solitarius.

Pharyngeal phase of swallowing

During the swallowing process, the oral cavity and pharynx are functionally interrelated. The distinction between the oral and pharyngeal phases is often unclear, as the whole *oropharyngeal phase* of swallowing is governed by the central pattern generator (CPG) for the human swallowing. The physiological sequence of this phase rapidly occurs and can be divided into three specific events.

1. The first aim is to prevent the bolus aspiration in the airway. This protection is obtained by different reflexes, regulated by the CPG. The closure of the velopharyngeal isthmus by the palate protects the nasal airway, whereas bolus aspiration in the laryngeal and tracheal airway is prevented by laryngeal elevation, a vital component of this protection system.

2. The tongue thrusts posteriorly to push the bolus throughout the pharynx and into the esophagus (XII CN) [12]. In the pharynx, the bolus is forced into the esophagus through a sequential wave of contraction of the pharyngeal constrictor muscles (X CN). The pharyngeal contraction facilitates subsequent pharyngeal clearance, with a profound shortening of the pharynx [12].

3. The upper esophageal sphincter (UES) relaxes and opens for the bolus transport into the esophagus. The UES is composed of the striated cricopharyngeus muscle. This muscle relaxes during a swallow and the UES opens to provide the bolus passage.

Then the pharyngeal phase of swallowing is completed and the UES closes until the next swallow [12].

1.2.3 Drooling physiopathology

Drooling, sialorrhea, ptyalism, and hypersalivation (or excessive salivation) are terms that have been used interchangeably throughout the literature and this has led to some confusion. Clinically, these four terms cause the same condition of saliva beyond the margin of the lips, however, they have a specific different physiopathology that should be known. The clear physiopathologic distinction is between drooling and hypersalivation. Drooling is an indication of an upset in the coordinated control mechanism of oro-facial and palate-lingual musculature leading to excessive pooling of saliva in the anterior mouth and resultant unintentional loss of saliva from the mouth [21]. Hypersalivation is excessive production of saliva and does not necessarily lead to drooling as the excess of saliva may merely be swallowed [21]. In drooling, there is rarely hypersalivation [10]. True hypersalivation is rare and can be induced by lesions or foreign bodies sited in the mouth, infections (such as rabies), iatrogenic causes, drugs, physiological factors (smell, sight, or thought of food), or idiopathic causes. Sialorrhea and ptyliasm are synonymous with hypersalivation as they have the same physiopathologic pattern [21]. Theoretically, drooling may result from the hypersecretion (*primary sialorrhea*) of saliva or, more commonly, impairment of swallowing (*secondary sialorrhea*). These problems may occur as consequences of different neurologic dysfunction in the form of motor deficits (e.g. cerebral palsy, peripheral neuromuscular disease, facial paralysis) or severe mental retardation [40].

Primary functions such as lip closure, intraoral tongue suction, and swallowing may be disturbed as a result of neurodevelopmental delay. People with neurological disorders experience concomitant disturbances of sensation, perception, cognition, communication, and behavior, and are also known to experience swallowing and feeding problems, particularly during childhood. The process of swallowing is highly complex and involves many muscles in the oral cavity, larynx, and esophagus; more than 30 nerves and muscles are involved in volitional and reflexive activities during eating and swallowing. During the process of eating, food must be masticated, formed into a bolus, and transported into the pharynx, primarily driven by the tongue. Fluids require initial containment and positioning of the ingested fluid in the oral cavity before its subsequent aboral propulsion into the pharynx. During this initial phase of swallowing, lip closure ensures bolus containment in the oral cavity, while cyclic tongue movements, coordinated with jaw movements, process solid foods. This oral component of swallowing is mostly voluntary and involves the lips, teeth, masticatory

muscles, and the tongue. Next, the pharyngeal component of swallowing will be initiated by stimulation of the superior laryngeal nerve, a branch of the cranial vagus nerve. This involuntary stage of swallowing is more reflexive. Whereas swallowing refers to the transport of a bolus (food, liquid, saliva) from the oral cavity to the stomach, feeding mainly describes the process of breastfeeding or bottle-feeding, the transition to solid foods, and/or the process of setting up, arranging, and bringing food or liquid from a plate or cup to the mouth. Feeding is not limited to the actual swallowing act but also incorporates child–caregiver interaction (e.g. responsive complementary feeding, verbal encouragement, the pressure to eat, and restrictive feeding practices by the caregiver) and child behaviors (e.g. self-regulatory eating practices and self-feeding skills). Swallowing problems (*dysphagia*) in neurological disorders may be characterized by poor tongue function having an impact on bolus transport, delayed swallow initiation with increased risk of unsafe swallowing or aspiration, reduced pharyngeal motility, and drooling due to reduced lip closure (sialorrhoea). Feeding problems present with prolonged feeding times or delayed progression of oral feeding skills and may lead to inadequate growth. Both swallowing and feeding problems are associated with dehydration, malnutrition, aspiration pneumonia, and even death [38].

In case of saliva overflow, disturbed coordination of tongue mobility is the most likely cause, because saliva production is generally accepted to remain within normal limits. Hypersalivation or hypersialorrhoea is rarely reported in children with neurological disorders. However, the causes of increased salivation are many. It can be an ictal finding in complex temporal-lobe epilepsy; it can be caused by a variety of medications or irritating factors, such as teething, smoking, and gastro-oesophageal reflux; or it can be a symptom in an affective disorder. Corrie E. Erasmus et al. [11] investigated whether drooling in children with cerebral palsy (CP) in general and in CP subtypes is due to hypersalivation. The objective of their case–control study was to determine whether saliva production in children diagnosed with CP who drool is within the normal range. In the study, the swab saliva collection method (swab test) was used, through which direct and exclusive salivary flow measurements are possible, taking dysfunctional oral motor control into account. Besides, they hypothesized that saliva secretion in children with dyskinetic CP is increased because of the added mechanical stimulation of the salivary glands as a result of hyperkinetic oral movements. This study supports the finding in previous studies that no hypersalivation exists in children with CP who drool. Dysfunctional oral motor control seems to be responsible for saliva overflow from the mouth, whereas increased unstimulated salivary flow may occur in children with dyskinetic CP as a result of hyperkinetic oral movements [11].

1.3 Etiology

1.3.1 Causes of drooling in children

The causes of drooling are listed in Tab. 1.3. Drooling may result from the hypersecretion of saliva or, more commonly, impairment of swallowing.

Causes of drooling in children
Developmental
Physiological • teething • nausea • foods • emotional • stimuli
Central nervous system and muscular disorders
Mental retardation
Rett syndrome
Other neurological disorders
Oropharyngeal lesions
Esophageal lesions
Gastroesophageal reflux
Drugs and chemicals
Familial dysauthonomia (*Riley-Day syndrome*)
Wilson disease

Table 1.3 List of possible causes of drooling in children [24].

Developmental causes In the first years of life, a mild degree of drooling can be considered as a normal condition. It is due to different factors, such as the infant's limited ability to swallow and the lack of front teeth. It increases around five to six months of age when salivation improves to its full capacity and it disappears by two or four years of age as a consequence of physiological maturity of oral motor dysfunction.

Physiological causes The salivary reflex is activated by several physiological stimuli. The first one is the eruption of teeth and in childhood drooling is a common sign of teething. Another physiological trigger is represented by some special foods, particularly sour or spicy

ones, which increase salivary flow. Salivation can also be stimulated by impulses arriving in the salivatory nuclei from higher centers of the brain. Marked salivation may occur when a person smells or eats his or her favorite foods. Hypersecretion of saliva may also occur with pleasurable sensation or anticipated pain, presumably through activation of higher centers [24].

Central nervous system and muscular disorders Children affected by neuromuscular disorders are at high risk to present drooling, because of their pathologic status. In this group of patients, the drooling physiopathology is meanly based on oral-motor dysfunction and swallowing disorders. Most of them present uncoordinated tongue movements, high tonus and spastic contraction of the pharyngeal-esophageal sphincter, dyscoordination between the pharynx and sphincter, and a lack of coordinated control of the head and neck musculature. Drooling is a common occurrence in myasthenia gravis, polymyositis, cerebral palsy, and other neurological disorders.

Mental retardation Drooling occurs in approximately 10% of children with mental retardation [24]. It is related to eating and swallowing problems, probably caused by a delay in the development of coordinated swallowing movement, inefficient and infrequent swallowing, lack of awareness of oral incompetence, and incomplete lip closure during swallowing.

Rett syndrome Rett syndrome is a progressive neurological disorder estimated to affect 1:10,000 to 1:15,000 of live females. Drooling is common in children with Rett syndrome. Drooling can be caused by hypersalivation or by difficulty with swallowing [24].

Other neurological disorders Angelman syndrome, Dravet syndrome, Goldenhar syndrome are frequently associated with drooling and hypersalivation.

Oropharyngeal lesions Pain and difficulty of swallowing may cause drooling in patients affected by oropharyngeal disorders. These include severe tonsillitis, peritonsillar or retropharyngeal abscess, epiglottitis, and damage to the oral or pharyngeal mucosa from caustic ingestion or direct trauma. Drooling may occur in acute infections involving the mouth or throat, such as gingivostomatitis from herpes simplex virus or coxsackievirus, which causes hypersecretion of saliva.

Esophageal lesions The esophageal phase of swallowing represents an important component of the whole process. An impairment at this stage can be responsible for both esophageal

dysphagia and drooling. Drooling may result from esophageal obstruction (esophageal stricture or foreign body), and esophageal injury (ingestion of caustics or corrosive acids).

Gastroesophageal reflux Episodic hypersalivation and drooling may result from gastroesophageal reflux. It is believed that stimulation of the esophagus by gastric acids excites an esophagosalivary reflex [24].

Drugs and chemicals Drooling is a common side effect of drugs that stimulate hypersalivation, such as morphine, pilocarpine, methacholine, haloperidol, and clozapine. Benzodiazepines may induce cricopharyngeal incoordination with impaired swallowing and drooling. Drooling may also be secondary to cocaine or phencyclidine intoxication. In the neonatal period, drooling may be a sign of withdrawal from maternal substance abuse [24].

Familial dysautonomia (*Riley-Day syndrome*) Drooling is common in children with Riley-Day syndrome. Drooling in familial dysautonomia is often due to difficulty in swallowing [24].

Wilson disease Wilson disease (*hepatolenticular degeneration*) can present with a variety of symptoms and signs. The most frequent ones are, in order of frequency, jaundice, dysarthria, clumsiness, tremor, drooling, gait disturbance, malaise, and arthralgia. Drooling in Wilson disease can be ascribed to dysfunction in the oral and pharyngeal phases of swallowing [24].

1.3.2 Neurological causes of drooling

Cerebral Palsy

The term *cerebral palsy* (CP) describes a group of movement and posture development disorders, with activity restrictions or motor disabilities caused by malformations or injuries that occur in the developing fetal or child's brain [10]. The disease primarily affects body movement and muscle coordination but may determine intellectual disabilities and behavioral abnormalities [10]. Sometimes there could be epilepsy and secondary musculoskeletal problems [10]. The motor disorder results from centrally mediated abnormal muscle tone: spasticity is the commonest abnormality. Thirty percent of affected children are unable to walk, 30% have several intellectual impairment, 28% have impaired or no speech and 12% are blind [34]. Worldwide, the prevalence of CP is 1-5 per 1000 live births, representing the most common cause of motor disability in children [10].

Causes and risk factors for cerebral palsy
Prenatal (80%) • Prematurity (<37 weeks of gestation) • Low birth weight (<2500 g) • Intrauterine growth restriction • Multiple births • Intracranial haemorrhage, white matter injury, and cerebral malformations • Maternal age >35 years • Severe maternal iodine deficiency • Associated birth defects • Maternal infection—for example, cytomegalovirus
Perinatal (10%) • Peripartum asphyxia • Maternal infection
Postnatal (10%) • Head trauma and hypoxia within the first two years of life • Meningitis • Intentional injury

Table 1.4 List of causes and risks factors for cerebral palsy [34].

Tab. 1.4 lists the risk factors for cerebral palsy. The exact cause of some cerebral palsies is still poorly understood and it may remain unclear in many children. Cerebral palsy epidemiology and etiology vary around the world and many developing countries present particular risk factors, such as cerebral malaria. In more than 80% of children, cerebral palsy is caused by brain lesions or maldevelopments. Prenatally, preterm, and very low birth weight are important risk factors. However, it is unclear whether low intrauterine growth represents a cause or a consequence of cerebral disability. Despite popular belief, peripartum asphyxia and hypoxia (hypoxic-ischaemic encephalopathy) account for only 10% of cases. Postnatal causes such as meningitis, near drowning, and intentional injury account for 10% [34].
The classification systems of cerebral palsy can be divided into two groups: those that describe physical motor abnormalities and those that describe function. A physical classification system is reported in Tab. 1.5. In this classification, the Surveillance of Cerebral Palsy in Europe collaboration only describes children's neurological status and does not provide information about their involvement in daily activities. The Gross Motor Function Classification System (GMFCS) is age-dependent and divides children into five groups

based on their ability to mobilize and their co-conjugation in society (Tabl. 1.6). Functional classification systems are more accurate, as they focus on what children can do, and are currently considered to be the ideal classification method.

Physically classification of tone and movement disorders in cerebral palsy
Topographic (distributional) description for spastic cerebral palsy • Unilateral • Bilateral
Classification of tone and movement abnormality *Spasticity* • Velocity dependent increased tone with hyperreflexia and upper neurone signs • Tone increased but not necessarily constantly *Dyskinetic* • Recurring, uncontrolled and involuntary movements that may be stereotyped • Tone abnormality varies • Dyskinetic cerebral palsy may be: Dystonic (hypokinesia and hypertonia) Choreoathetotic (hyperkinesia and hypotonia) *Ataxic* • Generalized hypotonia with loss of muscle coordination *Mixed forms* • No one tone abnormality and movement disorder predominates • A combination of spasticity with dyskinesia is the commonest mixed type

Table 1.5 The physical classification of cerebral palsy recommended by Surveillance of Cerebral Palsy Europe collaboration [34].

Gross motor function classification system
Level I - walks without limitation
Level II - walks without assistive devices, but with limitations (for example, limitations walking long distances, balancing, and using stairs)
Level III - walks a hand-held mobility device (for example, a k-walker frame or crutch)
Level IV - limited self mobility (for example, able to use a joystick activated powered wheelchair)
Level V - severe limited self mobility, child transported in a manual wheel chair (unable to use a joystick activated powered wheelchair)

Table 1.6 The gross motor function classification system is based on functionality and motor skills [34].

The diagnosis of cerebral palsy is based on a detailed antenatal and family history and a full examination. The key characteristic of these children is their failure or delay in achieving

the expected steps in motor development. A full neurological assessment should identify abnormalities in movements or muscle tone (excessive stiffness or floppiness). In the first five months of life, normal and awake infants present fidgety spontaneous general movements, defined as an ongoing stream of small, circular, moderate speed, and elegant controlled movements of the neck, trunk, and limbs in all directions. Absent or abnormal fidgety movements (exaggerated amplitude, speed, or jerkiness) at age 3 months is 95% sensitive and 96% specific for the development of neurological deficits, and when coupled with findings from magnetic resonance imaging in preterm babies, is almost 100% accurate in predicting cerebral palsy [34]. The diagnosis is usually made at two years of age.

Children with cerebral palsy present a wide range of clinical features and several associated problems may also predominate over motor symptoms, especially in the early years (Tab. 1.7). It is important to know these minor characteristics, to evaluate and treat them, and to facilitate early diagnosis. Feeding difficulties and sialorrhea may significantly alter children's quality of life. The prevalence of sialorrhea in CP is seldom studied and some authors reported a value of 10-58%. Currently, it is widely accepted that sialorrhea in children with CP is not caused by hypersalivation, but by oral-motor dysfunction, dysphagia, and/or intraoral sensitivity disorder. Several studies have shown a positive correlation between sialorrhea in children with CP and the following factors: difficulties in the formation of the food bolus, inefficient labial sealing, suction disorder, increased food residue, difficulty controlling the lips, tongue, and mandible, reduced intraoral sensitivity, reduced frequency of spontaneous swallowing, esophageal phase dysphagia, and dental malocclusion. Significant negative correlations have been found between sialorrhea and chewing capacity, as well as other swallowing skills in general. Other factors, all common in CP, influence the presence and severity of sialorrhea: open mouth position, inadequate body posture, particularly of the head, intellectual disabilities, emotional state, and degree of concentration [10].

Associated features of cerebral palsy and recommended management
Feeding difficulties • Related to GMFCS level: >90% in those with GMFCS level 4 or 5 cerebral palsy • Poor weight gain • Coughing and choking during mealtimes; long mealtimes • Recurrent chest infections • Gastrooesophageal reflux • Malnutrition • Premature death • Special diets, adjustment of food consistency and child positioning during mealtimes equipment to aid feeding, gastrostomy for unsafe swallow or to augment existing oral intake
Drooling • Impaired social interactions and participation • Secretions compromising airways • Behavioral therapies, biofeedback exercises, anticholinergic drugs, intragrandular botulinum toxin type A injections, surgical rerouting of salivary glands
Intellectual impairment, mental health, and behavioural problems • Affect 60% of children • Cognitive impairment • Anxiety and depression • Exclude pain and seizures as underlying causes; review treatment and stop unnecessary drugs (especially sedatives); encourage partecipation and indipedence with all aspects of life; offer counseling for emotional support and psychological challenges; consider formal psychiatric assessment
Seizures • Affect 30-40% of children • Head protection orthosis, drugs for control and monitoring
Communication difficulties • Impaired social interactions and participation • Speech therapy, use of (sign language) and eye gaze for communication cards and books, electronic communication aids
Impaired vision and hearing • Affects 12% of children • Retinopathy of prematurity • Visual field defects • Myopia • Strabismus, which may lead to amblyopia, and blindness • Hearing impairments • Screen for in all children with developmental impairment; retinopathy of prematurity and squint may require surgery
Abnormal pain and touch sensations • Sensory and physical stimulation programs and oral drugs
Bladder dysfunction • Incontinence or retention secondary to impaired motor control of bladder muscles • Nappies or padding in underwear, biofeedback exercises, drugs, urological procedures
Sleep disturbances • Commonly secondary to pain from a variety of causes • Assessment and treatment of underlying cause, counselling and emotional support for psychological challenges
Constipation

Table 1.7 Clinical features of cerebral palsy [34].

Dravet Syndrome

Dravet syndrome (DS) (OMIM 607208) is a rare infantile-onset epileptic encephalopathy associated with global developmental delays and intractable epilepsy. It is associated with mutations of SCN1A gene in 75% of cases. Hallmarks of the disease are frequent prolonged seizures, development delays, speech impairment, and motor/orthopedic issues. Comorbidities of the syndrome include dysautonomia, nutrition issues, characteristics of autism, and a high rate of sudden unexpected death in epilepsy (SUDEP) [42, 14]. Dravet syndrome affects approximately 15700 individuals in the United States but its incidence is not well known. In the most recent study in Spain, it is reported a prevalence of 1.4% in epilepsy children aged $<$ 15 years. However, DS is still considered a rare condition, even if its incidence has increased in the last decade [14].

The first name the syndrome was given is "Severe myoclonic epilepsy of infancy" (SMEI), to describe a severe and rare epileptic encephalopathy with pharmacoresistence, drop attacks, episodes of status epilepticus and intellectual disability, and to distinguish it from Lennox-Gastaut syndrome (LGS), the most common severe epilepsy of childhood. Dr. Charlotte Dravet, over 30 years ago, noticed that some children wrongly labeled as LGS exhibited massive myoclonus with photosensitivity and had had febrile seizures (FS) from the first year of life, thus pointing to a previously overlooked condition. Later, when it appeared that myoclonus was missing in over half the cases, the condition received the eponym of DS. Since then, its molecular basis has been identified [13]. The most common etiology identified in patients with clinical Dravet syndrome is a de novo, heterozygous, the loss-of-function variant in SCN1A, the gene encoding the pore-forming (α) subunit of the voltage-gated sodium channel Nav1.1 [14]. SCN1A haploinsufficiency producing NaV1.1 dysfunction mainly affects GABAergic neurons. In cortical interneurons, it explains epilepsy, in cerebellum the ataxia, in basal ganglia and motor neurons the crouching gait, in hypothalamus the thermodysregulation and sleep troubles, and dysfunction in all these structures contributes to psychomotor delay [13]. Among individuals with a pathogenic SCN1A, a range of phenotypes is possible, with different prognosis. Truncation is more often associated with Dravet syndrome, while missense variants more often result in less severe phenotypes, characterized by generalized epilepsy with febrile seizures plus (GEFS+). However, genotype-phenotype correlation is predictably more complex for interpreting missense variants, as not only the location but also the nature of the amino acid substitution impact disease phenotype [14]. Missense variants specifically localized to the pore region have been associated with earlier seizure onset, presence of ataxia, and a more severe (i.e. higher likelihood to be refractory) epilepsy phenotype. Yet, there are also missense pore variants to which a GEFS +

phenotype has been attributed [14]. Tracy S. Gertler et al. [14] sought to evaluate the genetic diversity and correlative seizure phenotype, comorbidities, and response to antiepileptic therapies of patients with clinically diagnosed Dravet syndrome seen in a tertiary care center. The goal of this study is to examine genotype-phenotype correlations and to ascertain if specific antiepileptic therapies may be more effective based on genetic test results alone. As results, of the 96% of Dravet syndrome patients with pathogenic SCN1A variants subdivided by missense or truncating variant, there is no difference in clinical presentation. Response to antiepileptic therapies does not differ by genotype with regard to the medication class [14].

Dravet syndrome begins during the first year of life in a normal baby who presents with one convulsive seizure [5]. The first seizure is typically clonic, generalized, or unilateral, triggered by fever and longer than a simple febrile seizure. However, some variability in the mode of onset has been reported. Convulsive seizures can occur without fever in from 28% to 35% and 61% of the patients. These afebrile seizures usually occur in the context of vaccination, an infectious episode, after a bath, and later on, they were associated with febrile seizures. These seizures, with or without fever, tend to be prolonged, lasting longer than 20 minutes, in 25% to 49% of the patients, and to evolve into status epilepticus [5]. At this stage of the disease, EEG is usually normal both while awake and during sleep. In some patients, EEG recording can show generalized spike waves (SWs), either spontaneous or elicited by the intermittent photic stimulation (IPS). Rhythmic theta activities at 4–5 Hz can be present in the centroparietal areas and over the vertex. The first seizure is often considered to be an accidental episode. However, between age 1 and 4 years, other seizure types appear, simultaneously with slowing of the development, and the picture becomes characteristic of a steady-state [5]. In steady-state, patients with Dravet syndrome have multiple seizure types: (1) convulsive seizures consisting of generalized clonic seizures (GCS), generalized tonic–clonic seizures (GTCS), or alternating unilateral clonic seizures; (2) myoclonic seizures; (3) atypical absences and obtundation status; (4) focal seizures, with or without secondary generalization; or (5) rarely, tonic seizures.

1. Convulsive seizures, apparently generalized or unilateral, are present throughout the evolution in all patients. Most seizures are secondarily generalized after a brief focal onset. Unilateral seizures present different characteristics at different ages. In the youngest patients, they correspond to hemiclonic seizures and often evolve to status. In older patients, they are shorter.

2. Myoclonic seizures appear between the ages of 1 and 5 years. Their intensity is variable. When massive, they involve all muscles and they are so violent that the objects held by

the child fall. Sometimes, they involve only the axial muscles (head and trunk), giving a small movement forward or backward, known as *head nodding*. They also show wide variability in the temporal pattern. In most cases, they are isolated or grouped in brief bursts (1-3 s) and occur several times a day, often incessantly. Conversely, in some children, they are observed only on awakening or in the minutes or hours preceding a convulsive seizure. They persist during drowsiness and disappear during slow sleep. The occurrence of myoclonic status is rare.

3. Atypical absence seizures can appear between 4 months and 6 years of age, together with myoclonic attacks, or later on, up to the age of 12 years [5]. Their duration varies from 3–10 s. They are characterized by impairment of consciousness, either isolated or accompanied by a more or less obvious myoclonic component such as rapid eyelid myoclonia, realizing an *eye fluttering*, *head nodding*, and forehead myoclonic jerks. Convulsive seizures can initiate, occur during, or terminate this status [5].

4. Focal seizures consist of motor seizures or seizures with prominent autonomic symptoms. They occur from 4 months to 4 years, in 43–78.6% of patients. The seizures occur in patients who have one or several foci, in the posterior and frontal brain areas. The two focal seizure types can secondarily generalize [5].

5. Tonic seizures are unusual in DS.

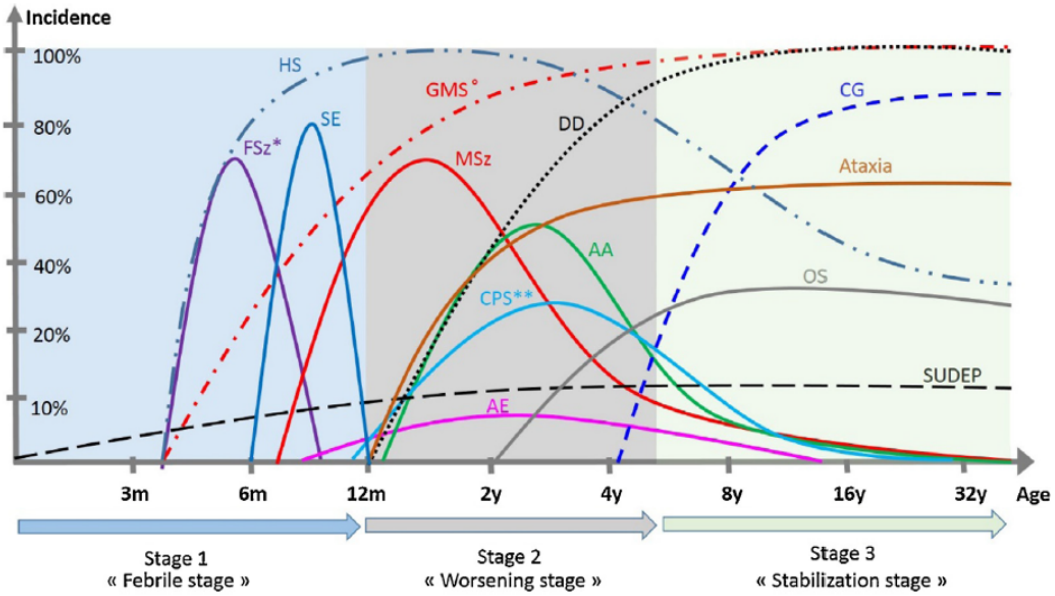


Fig. 1.4 Schematic representation of clinical manifestations of Dravet syndrome and their relative incidence according to age. From Svetlana Gataullina, “From genotype to phenotype in Dravet disease” [13]. FSz, complex febrile seizures; HS, hyperthermia sensitivity; SE, convulsive status epilepticus; GMS, generalized motor seizures; MSz, myoclonic seizures; AA, atypical absence; CPS, complex partial seizures; OS, obtundation status; AE, acute encephalopathy; DD, developmental delay; CG, crouching gait; Ataxia; SUDEP, Sudden unexpected death in epilepsy; Moderate fever for 60%; mostly clonic generalized and unilateral motor seizures; **Difficult distinction between atypical absences and complex partial seizures without ictal EEG recording, so their precise incidence is unknown; Including generalized tonic–clonic and unilateral seizures

Steady-state is characterized by a wide range of clinical aspects, which are resumed in Tabl.1.8 [42]. This clinical variety emphasizes that Dravet syndrome may be better viewed as a disease of the central nervous system with nonepileptic manifestations rather than merely an epilepsy syndrome. While research and treatment often focus on managing refractory seizures with antiepileptic drugs (AEDs), other issues are common and may not be adequately addressed by the medical community. Health-related quality of life (HRQOL) is typically lower in patients with DS than in both the general population and in patients with epilepsy not classified as DS. At the very onset, the infants are apparently normal. The neurologic signs appear progressively, simultaneously with the developmental delay, but are not observed in all patients. The signs consist of hypotonia, ataxia (60%), pyramidal signs (20%), uncoordinated movements, and interictal myoclonus. The association of hypotonia and ataxia leads to a particular way of walking and running, as if the children had *"spaghetti legs"*, as written by a mother. Kyphoscoliosis and club feet are frequent, worsening with age,

and are responsible for walking difficulties. Facial muscle hypotonia can cause chewing and swallowing difficulties, which are considered to be the main causes of sialorrhea and other digestive problems [5].

Clinical features of Dravet syndrome
Epilepsy, neurologic signs and movement disorders hypotonia, ataxia, pyramidal signs, uncoordinated movements, myoclonus, gait disturbances
Cognitive disorders, psychiatric issues and autistic traits cognitive deficit, behavioural disturbances, obsessions, aphasia, delayed language, anxiety, depression
Dysautonomia issues difficulty with temperature regulation, lack of sweating
Sleep disorders sleep disturbances, nocturnal seizures, insomnia, premature awaking
Cardiac issues long QT intervals, bradycardia, tachycardia
Hearing and vision issues pattern sensitivity, photosensitivity, hyperacusis, frequent blinking
Dental and orthopedic issues kyphoscoliosis, club feet, osteopenia, bone fractures
Bowel and digestive issues incontinence, constipation, appetite disturbances
Urinary tract issues nephrocalcinosis
Blood issues low platelets, vitamin D deficiency, iron deficiency
Infection/immunity issues frequent/chronic otitis media/bronchitis/pneumonia, allergies
Metabolism and endocrine issues delayed/precocious puberty
*Sudden death (SE)**

Table 1.8 List of Dravet syndrome comorbidities. *Mortality rate is high, reaching 10-18% of patients, with a peak at 3-7 years. SE used to be a significant cause of death (36%), but has decreased with improved diagnosis and treatment SUDEP is presently the main cause (56%) with two peaks, at 1– 3 and over 18 years, without evidence of worsening of epilepsy [42].

Rett Syndrome

Rett syndrome (RTT, OMIM 312750) is an X-linked neurodevelopmental disorder that mostly affects females and is the second most common cause of severe intellectual disability in females after Down syndrome [15]. The Rett syndrome was first described in 1966 by Andreas Rett, who published the first English language account of the condition in 1977 as *"Cerebral atrophy with hyperammonaemia"*. Rett syndrome became better known when Hagberg et al. described 35 affected girls in 1983. The incidence or prevalence among females has been estimated as 1 in 10-15 000 (incidence) in Scotland, 1 in 15 000 (prevalence) in Sweden, 1 in 20 000 (prevalence) in Dakota, USA, and 1 in 22 800 (prevalence) in Texas, USA. RTT, therefore, accounts for 2-3% of severe mental handicaps and perhaps 10% of profound handicaps in females. Despite its importance, however, the pathogenesis of RTT remains obscure. It is most likely to be an X-linked dominant disorder, lethal in hemizygous males but this is not certain [8]. The major causative gene is methyl CpG binding protein 2 (MECP2).

RTT is a neurodevelopmental disorder, which means that the course of the disorder changes over time when the motor and cognitive development should be progressing [8]. In 1985, Hanefeld separated the progression of the disease into four distinct stages known as Stage I to Stage IV (Tabl.1.9) [8]. *Stage I* consists of the early period of life, between 6 and 18 months of age. It is characterized by a delay or stagnation in development. In *Stage II* the stereotypic hand movements, a hallmark of RTT, become evident and girls lose acquired skills, such as language and gross motor skills. Stage II ends at 4 years of age when it is followed by *Stage III*, also called the *pseudostationary age*. Girls partially regain some social and motor skills and their phenotype stabilizes. The *late motor deterioration stage* or *Stage IV* can last for years or decades and is characterized by reduced mobility, muscle weakness, rigidity, and spasticity [15].

Clinical stages of Rett syndrome
Stage I. Early onset stagnation • Onset age 5-18 months • Developmental progress delayed but still not significantly abnormal. Postural delay, hypotonia, and bottom shuffling are common • Often only diagnosed in retrospect • Duration: weeks or months
Stage II. Rapid developmental regression • Onset age 1-4 years, may be abrupt • Loss of acquired skills (hand use, voice, communication, active play) • Gross motor functions may be relatively preserved • Temperament may change, and sometimes the girl is distressed • Autistic features appear, including stereotypies • Eye contact is often preserved • Significant developmental delay and dementia become apparent • Breathing irregularities and seizures may be noted • Duration: weeks to months, possibly one year
Stage III. Pseudostationary period • Onset 2-10 years • Some restoration of communication, "wake up" period • Ambulation preserved, but unapparent, slow neuromotor regression • Prominent hand apraxia/dyspraxia • Seizures are common • Duration: years to decades
Stage III/IV • Describes girls whose regression has ceased but who are not ambulant • If a girl then learns to walk she is reassigned to stage III • If she is still unable to walk at age 10, she is reassigned to stage IV
Stage IV. Late motor deterioration • Onset when stage III ambulation ceases, often in teenage years • Severe physical disability, wasting, spasticity, dystonia and bradykinesia, distal distortions • Complete wheelchair dependency • Duration: decades
Subclassification of stage IV • Stage IVa: previous walkers (ex-stage III) • Stage IVb: never ambulant (ex-stage III/IV)

Table 1.9 Clinical stages of Rett syndrome according to Hanefeld and revised by Witt-Engerstrom, list and description [8].

RTT has been diagnosed only on a clinical base since the first report in 1966. When the Zoghbi laboratory in 1999 identified the MECP2 gene as the responsible gene for the syndrome, the genetic analysis was included in RTT diagnosis. However, 5% of patients who meet the diagnostic clinical criteria do not present mutations in MECP2. As a result, the diagnosis of RTT is based on both clinical and molecular findings. Around 95% of classical RTT cases and 75% of atypical RTT cases have mutations in MECP2. Although the majority of RTT patients have mutations in the MECP2 gene, mutations in other genes are associated with RTT, including cyclin-dependent kinase-like 5 (CDKL5), Forkhead box protein G1 (FOXG1), myocyte-specific enhancer factor 2C (MEF2C), and transcription factor 4 (TCF4) (Fig.1.5). MECP2 is a member of the methyl binding domain (MBD) family, a key epigenetic modulator abundantly expressed in the brain. Mutations in MECP2 impair neuronal development, as MECP2 plays an important role in neuronal function. Over 900 mutations have been identified within MECP2, with 518 being pathogenic. The pathogenic mutations are especially localized in three major domains: the methyl binding domain (MBD), the transcriptional repression domain (TRD) and the nuclear localization signal (NLS) domain [15].

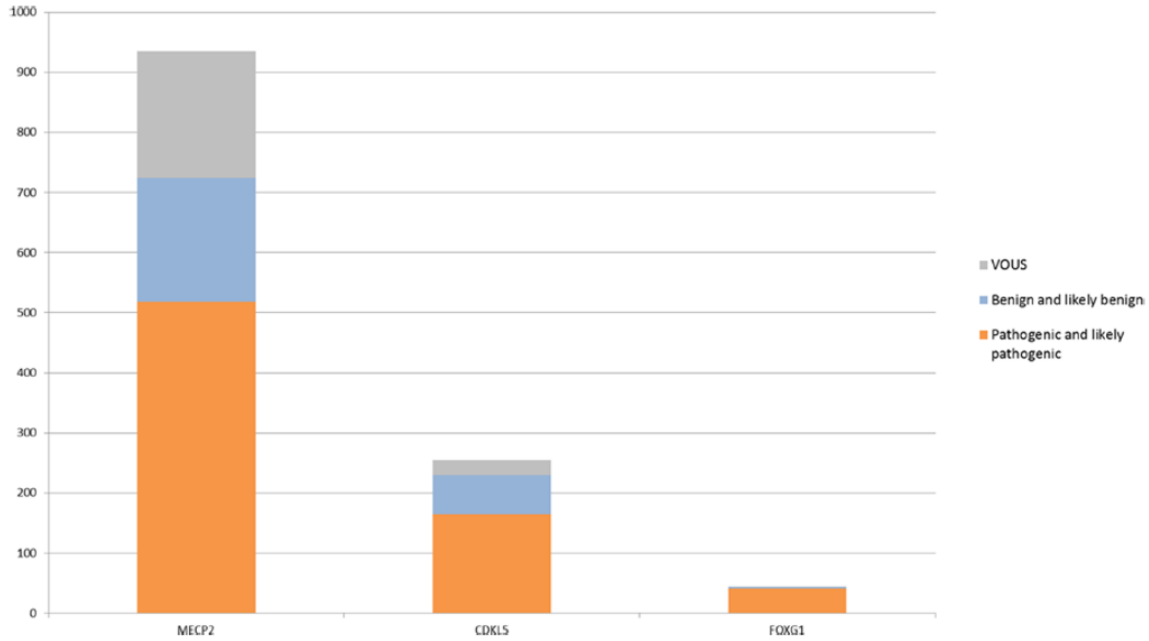


Fig. 1.5 Distribution of pathogenicity of variants in MECP2, CDKL5, and FOXG1 genes. From: Wendy A. Gold, “Rett Syndrome: A Genetic Update and Clinical Review Focusing on Comorbidities” [15]. This graphic reports percentage of pathogenicity of three different genes (MECP2, CDKL5, FOXG1) and shows that MECP2 is the principle gene involved in Rett syndrome.

Rett syndrome is almost always sporadic in a family, because almost all cases represent new mutations, except in the case of monozygotic twins, who are concordant for RS. However different models of inheritance have been proposed to explain the rare cases of multiple RS patients in the same family. At first, it was proposed that RS could be an X-linked dominant, male lethal (XDML) disorder, but a few families with two affected females have been reported. The hypothesis of a mosaicism model with X inactivation is not supported by both lymphocytes and postmortem brain studies. Other models of inheritance that have been proposed include uniparental disomy and metabolic interference. Finally, given that almost all cases would represent new mutations, no deficit of males or excess of females or miscarriages would be expected in the families of girls with RS, except perhaps in the very few families with more than one affected person [8].

The great variability of RTT clinical presentation has resulted in the revision of the clinical diagnostic criteria over the years. The first set of clinical criteria was established in 1983 by Hagberg and colleagues. The following publications included reports on atypical RTT, such as the milder clinical form known as the *Zappella variant*, the *preserved speech variant* where patients have some degree of speech, the *frome fruste variant*, the early onset seizure form (also known as the *Hanefeld variant* or *early seizure variant*), and the very early onset symptom variant known as the *congenital variant* [15]. The clinical diagnostic criteria have been revised first in 1994 and then in 2002, in order to take into account the emerging atypical cases and to make a rapid diagnosis. Finally, in 2010, a further set of criteria were developed to further define and simplify the diagnosis (Tabl.1.10) [28]. Neul criteria are now the diagnostic criteria most commonly used for the identification of new cases of RTT. The diagnosis is excluded if there is a history of brain injury secondary to trauma, neurometabolic disease, or severe neurological infections. The diagnosis is also excluded if there is grossly abnormal psychomotor development within the first six months of life. Before the groundbreaking discovery that mutations in MECP2 caused RTT in 1999, the diagnosis of RTT was based solely on clinical diagnostic criteria. However, despite this discovery, due to the complex nature of the disorder, the diagnosis of RTT still relies, to a large extent, on the clinical diagnostic criteria and the exclusion of differential diagnoses [15].

Revised diagnostic criteria for Rett syndrome (2010)
Consider diagnosis when postnatal deceleration of head growth observed
Required for typical or classic RTT 1. A period of regression followed by recovery or stabilization 2. All main criteria and all exclusion criteria 3. Supportive criteria are not required, although often present in typical RTT
Required for atypical or variant RTT 1. A period of regression followed by recovery or stabilization 2. At least 2 of the 4 main criteria 3. 5 out of 11 supportive criteria
Main criteria 1. Partial or complete loss of acquired purposeful hand skills 2. Partial or complete loss of acquired spoken language 3. Gait abnormalities: impaired (dyspraxic) or absence of ability 4. Stereotypic hand movements
Exclusion criteria for typical RTT 1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems 2. Grossly abnormal psychomotor development in first 6 months of life
Supportive criteria for atypical RTT 1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis 7. Growth retardation 8. Small cold hands and feet

Table 1.10 Neul criteria for the diagnosis of Rett syndrome; they represented the most recommended criteria that are considered nowadays [28].

As described above, RTT is a severe neurodevelopmental disorder characterized by the loss of language skills, fine and gross motor skills, communication skills, deceleration of head growth, and the development of stereotypic hand movements occurring after a period of apparently normal development. However, the spectrum is broad, with girls developing

comorbidities at different stages. Comorbidities recognition and study are the keys to improve patients' quality of life. Comorbidities often include seizures, breathing disturbances with hyperventilation and/or apneas, gastrointestinal complications, gait disturbances, and scoliosis, which in combination make the management of RTT very complex. Among gastrointestinal problems, the most common disturbances are gastroesophageal reflux, air swallowing with abdominal distension, and chronic constipation. Some girls experience abdominal pain due occasionally to gallbladder disease. The lack of oral motor control frequently results in feeding difficulties and poor weight gain, which may lead to nutritional deficiencies that require close monitoring and in some gastrostomy tube placement is required to maintain body weight and general health. Bone health is a major concern as most girls have osteoporosis and develop scoliosis. Approximately 10% of girls with scoliosis require surgical intervention. Increased muscle tone associated with dystonia, contractures, and rigidity, along with other Parkinsonian features is common in the later stages of the disorder. Girls with RTT commonly have breathing dysregulation, including hyperventilation and breath-holding episodes when awake. Behavioral abnormalities have long been recognized as a fundamental feature of RTT, particularly autistic behavior which arises during the period of regression and can persist into the post regression period. A high prevalence of anxiety and mood disturbances, such as repetitive self-injury, screaming episodes, abrupt mood changes, and inconsolable crying are also prevalent. Fear and anxiety are also common in RTT patients, with these behaviors being inversely associated with mutation type/disease severity. For example, individuals with mutations resulting in a milder phenotype (p.Arg133Cys, p.Arg294, and large deletions) are more likely to experience mood problems and higher levels of anxiety and those with mutations that cause a more severe phenotype (p.Thr158Met and p.Arg168). Although RTT is not considered a neurodegenerative disorder, recently it has been identified that, for most mutation types, regardless of the initial severity of the mutation, clinical severity becomes progressively worse with age. This demonstrates that the MECP2 mutation type is a strong predictor of disease severity, thus, careful attention needs to be applied to each comorbidity so that clinicians and families can better prepare for the needs of patients with RTT [15].

Overall survival and quality of life are improving in RTT with the development of guidelines for the management of specific comorbidities. Drooling is a common problem in girls with Rett syndrome; excessive drooling is the result of the severe motor deterioration that causes swallowing difficulties. Hypersalivation can contribute to swallowing difficulties, only in the way of drug adverse effects. Children and adults with Rett syndrome develop several drooling consequences, which can cause discomfort due to hygienic problems and may

complicate with oral and respiratory dysfunction [2]. Oral health of the population with Rett syndrome is seriously compromised. María-Cristina Fuertes-González et al. [16] performed a prospective, observational case-control study to describe RTT oral symptoms. The most frequent oral habit in the patients with RS turned out to be diurnal bruxism, followed by stereotyped tongue movements and oral breathing. The caries scores were lower in the RS population than in the control group, but patients with RS showed greater periodontal alterations and a greater prevalence of drooling, dental wear, high-arched palate, and anterior open bite [16]. The only way to prevent oral issues is drooling management, as described in "The treatment of hypersalivation in Rett Syndrome with Botulinum Toxin: Efficacy and Clinical Implications". In this study, Pia Bernardo et al. [2] evaluate the response to treatment with botulinum toxin for hypersalivation and trie to identify possible benefits of saliva reduction on oral motor and respiratory disorders of patients with RTT: botulinum toxin injection in salivary glands is reported to be effective in both reduce saliva production and improve patients' quality of life [2].

According to recent works, the study of the composition of saliva in patients with RS can help in understanding the pathophysiology of the syndrome. Immune dysregulation may play a role in the development of Rett syndrome and measurements of salivary cytokines may be considered as an alternative approach to measurement in blood and serum and a possible indicator of immune dysregulation in RTT. Concentrations of several salivary cytokines (IL-1β, IL-6, IL-8, IL-10, GM-CSF, TNF-α, and VEGF) are increased in RTT and the same cytokines showed significant positive correlations with clinical severity scores [6].

Angelman Syndrome

Angelman syndrome (OMIM 105830) is a severe neurodevelopmental disorder first described in England by Dr. Harry Angelman. In 1965, the pediatrician noticed three children with similar features, consisting of severe learning disability, a seizure disorder with a characteristic EEG pattern, absent speech, ataxic jerky movements, and a happy, sociable disposition [4]. Angelman went on to publish his landmark report "'Puppet' Children" in 1965 with the discovery of what became known as *happy puppet syndrome*. This name was based on the described phenotype, with frequent paroxysms of laughter and ataxic movement. This nomenclature has historical significance but is no longer used, as the name Angelman syndrome was introduced in 1982 [41].

Angelman syndrome has a prevalence estimates ranging from 1 in 20,000 to 1 in 12,000 [41].

Angelman syndrome is caused by loss of function of the ubiquitin–protein ligase E3A (UBE3A) gene, which, in neurons, is expressed from the maternal chromosome 15 only [4]. The clinical expression of UBE3A gene is regulated by the imprinting phenomenon. Genetic imprinting is a process of transcription regulation based on a specific parental inheritance pattern. One allele on either the maternally or paternally inherited chromosome remains active, whereas the homologous allele inherited from the other parent is epigenetically suppressed. The paternal copy of UBE3A is epigenetically silenced through the differential methylation of an imprinting center, whereas the maternal allele remains active. Angelman syndrome is a neurogenetic imprinting disorder, which results from the loss of maternal UBE3A expression. Because the paternal allele is silent in neurons, lost maternal expression results in a deficit of UBE3A in the central nervous system [41].

Clinical features in Angelman syndrome
A. Consistent (100%) • Developmental delay, functionally severe • Movement or balance disorders, usually ataxic gait or tremulous movements of limbs • Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotoric behavior • Speech impairment, no or minimal use of words; receptive and nonverbal communication skills higher than verbal skills
B. Frequent (more than 80%) • Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (2 S.D. of normal OFC) by age 2 years • Seizures, onset usually at <3 years of age • Abnormal EEG, with characteristic pattern
C. Associated (20-80%) Flat occiput, occiptal groove, protruding tongue, suck/swallowing disorders, feeding problems or truncal hypotonia during infancy, prognathia, wide mouth, wide-spaced teeth, frequent drooling, strabismus, hypopigmented skin/hair/eyes, hyperactive, deep tendon reflexes, uplifted and flexed arm position, wide-based gait with pronated or valgus-positioned ankles, increased sensitivity to heat, abnormal sleep-wake cycles and diminished need for sleep, attraction to or fascination with water, abnormal food-related behaviors, obesity (in the older child), scoliosis, constipation

Table 1.11 List and description of Angelman syndrome clinical features [41]. EEG, electroencephalogram; OFC, occipitofrontal circumference; S.D., standard deviation.

The principal clinical features of Angelman syndrome are summarized in Tab.1.11 [41]. Hallmarks of the syndrome are the phenotypic features described by Angelman, which remain an integral part of the diagnosis, and include developmental delay, movement or balance disorders, limited speech, and distinctive behavior. Moreover, children affected by Angelman syndrome present a wide range of additional features, which generally persist in adulthood.

At 6 months of age they develop a psychomotor delay, usually associated with feeding difficulties and drooling, caused by muscular hypotonia. The prevalence of hypotonia may decrease through childhood but 22% may manifest persistent hypotonia and drool. In the first 3 years of life, the children often develop microcephaly, which is absent at the time of birth and does not represent a diagnostic criteria of the syndrome. Epilepsy generally appears at 1-3 years of age, with no distinctive seizure phenotype. EEG can show relatively specific findings, including diffusely distributed, high-amplitude slow waves, accompanied by sharp and slow waves known as a delta pattern, all of which suggest an epileptiform activity. EEG abnormalities can be profound even in the absence of clinical seizures [4]. Most children with Angelman syndrome present walking abnormalities. Generally, they do not walk until they are 3-4 years of age. The gait is characteristic, with a *marionette-like* quality associated with a wide-based stance with pronated ankles [4]. About 10% of individuals with this condition do not achieve ambulation and are wheelchair-bound [4]. Children affected by Angelman syndrome typically perform a specific behavioral phenotype, with excessive laughter and happy grimacing, often associated with a protruding tongue [4]. Children with Angelman syndrome are well known to have nighttime awakenings and have an apparently diminished total sleep time [4].

The clinical diagnosis of Angelman syndrome needs to be confirmed by a genetic analysis. The first molecular test for patients suspected of having Angelman syndrome is DNA methylation testing. Unaffected individuals have an unmethylated paternal allele and a methylated maternal allele at UBE3A locus, whereas in individuals with Angelman syndrome only a paternal unmethylated allele can be detected [4]. DNA methylation testing only identifies individuals affected by Angelman syndrome who present a methylation defect (80%). However, individuals with a UBE3A mutation have a normal methylation pattern. Thus, if Angelman syndrome is strongly suspected in the absence of methylation defects, this gene needs to be sequenced [4].

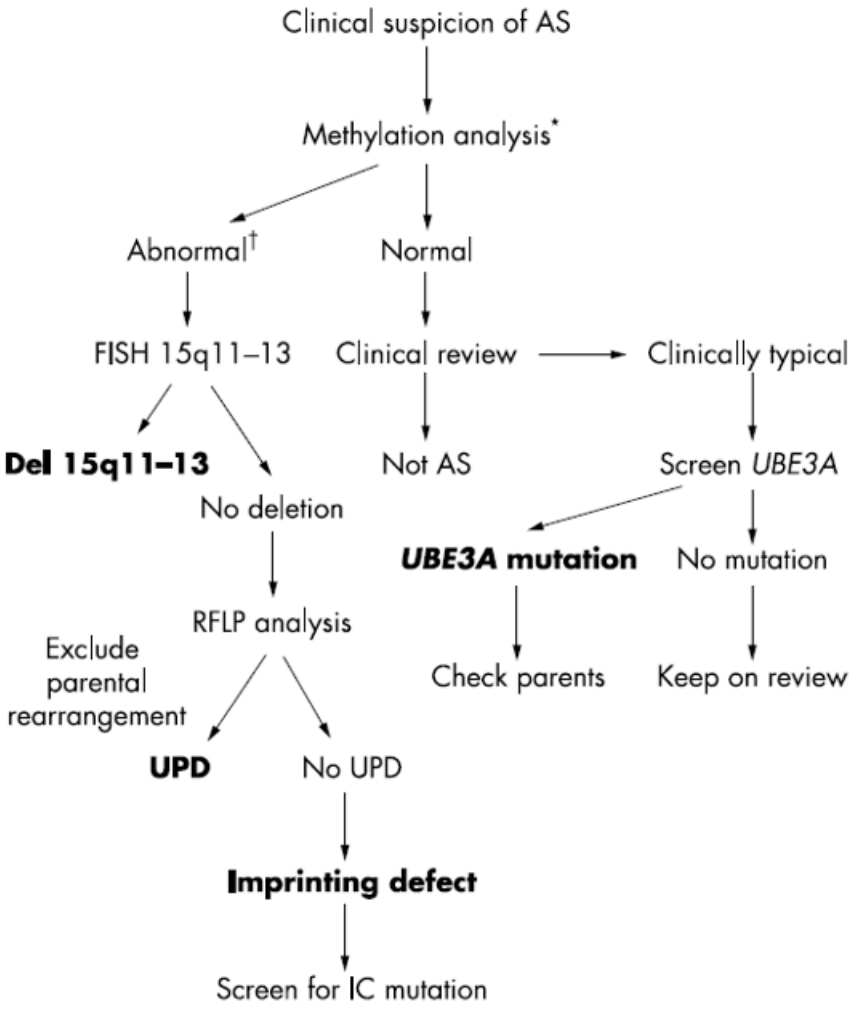


Fig. 1.6 Simple algorithm for genetic testing in Angelman syndrome. *In practice blood is usually taken for methylation analysis and FISH analysis at the same time. An abnormal result is where the methylation analysis shows an absent or reduced maternal band. FISH, fluorescence in situ hybridization; AS, Angelman syndrome; RFLP, restriction fragment lenght polymorphism; UPD, uniparental disomy; IC, imprinting center. From: J. Clayton-Smith, L. Laan, "Angelman syndrome: a review of the clinical and genetic aspects" [9].

	Seizures	Severe Cognitive Impairment	Absent Speech	Ataxia /Wide-Base Gait	Hypotonia	Sleep Problems	Microcephaly	Frequent Laughter /Smiling	Clinical Characteristics Not Typically Observed in Angelman Syndrome
Mowat-Wilson syndrome	●	●	●		●		●	●	Congenital heart disease
Pitt-Hopkins syndrome	●	●	●	●	●		●	●	Hyperventilation and apnea
Christianson syndrome	●	●	●	●		●	●	●	Ophthalmoplegia (X-linked dominant)
Rett syndrome	●	●		●		●	●		Loss of acquired skills (X-linked dominant)
Prader-Willi syndrome	●				●	●			Short stature, hypogonadotropic hypogonadism
Chromosome 2q23.1 deletion syndrome	●	●	●	●	●	●	●		Sandal gap between the first and second toe, hypoactivity
Phelan-McDermid syndrome	●	●	●		●				Tall stature, ptosis
MECP2 duplication syndrome	●	●	●	●	●	●	●		Limited facial expression (X-linked recessive)
Adenylosuccinate lyase deficiency	●	●	●	●	●		●	●	Muscle wasting
Methylene tetrahydrofolate reductase deficiency	●	●		●			●		Homocystinemia
Congenital disorders of glycosylation	●	●		●	●				Hyporeflexia, coagulopathy

Fig. 1.7 Differential diagnosis of Angelman syndrome. From: Ronald L. Thibert, "Neurologic Manifestations of Angelman Syndrome" [41].

Goldenhar Syndrome

Goldenhar syndrome (hemifacial macrosomia or HFM; OMIM 164210), also known as oculo-auriculo-vertebral syndrome (OAVS), is a rare congenital defect caused by development defects of the first and the second brachial archs. The disorder is characterized by a wide spectrum of congenital anomalies involving cardiac, renal, and central nervous systems [35].

The incidence of this disorder ranges from 1: 3,500 to 1 : 5,600 live births, with a male-to-female ratio of 3:2 [17].

Goldenhar syndrome has a multifactorial etiopathology that includes genetic and environmental factors. Most cases are sporadic, but autosomal dominant, autosomal recessive, and multifactorial models of inheritance have been suggested [35].

Goldenhar syndrome is also known as *oculo-auriculo-vertebral syndrome* for its classical triad of ocular, auricular, and vertebral disturbances. It was first described by Von Arlt in 1845, but Goldenhar gave a more detailed definition of the syndrome, in 1952. He noticed a condition characterized by a combination of several anomalies such as dermal epibulbar tumors, periauricular appendices, and malformation of the ears. Children affected by Goldenhar syndrome may also present heart diseases, disturbances of the central nervous system, and other visceral anomalies. The clinical pattern presents such a great variability

that it was given different and various synonyms: Goldenhar Gorlin syndrome, first and second branchial arch syndrome, oculo-auriculo-vertebral dysplasia, facio-auriculo-vertebral spectrum.

However, the most recognizable feature of Goldenhar syndrome is the presence of facial abnormalities. This symptom varies from a mild asymmetry of the face to a severely underdeveloped facial half with orbital anomalies. Microtia and auricular tags are found in 100% of the cases. Approximately 50% of the cases have combined conductive and sensorineural hearing loss. One of the most common craniofacial defects in Goldenhar syndrome is unilateral hypoplasia of the mandible on the affected side. This syndrome also affects dentofacial structures, inducing a cleft lip and palate, tongue cleft, unilateral tongue hypoplasia, a highly arched palate, hypoplasia of the maxillary and mandibular arches, micrognathia, gingival hypertrophy, supernumerary teeth, enamel and dentine malformations, and delayed tooth development. Some patients exhibit hypoplastic development of the facial expression muscles and asymmetric development of the mastication muscles on the affected side. Agenesis of the salivary glands or salivary fistulas and velopharyngeal insufficiency has also been observed [17].

1.4 Epidemiology

The overall prevalence of significant chronic drooling in childhood is put at up to 0.6% [36]. The commonest population group with severe and persisting difficulty is children with quadriplegic cerebral palsy where the prevalence rate is as high as 30– 53% [36]. The prevalence of drooling has been studied mainly in CP patients since sialorrhea is particularly frequent in this type of population. The estimated prevalence in cerebral palsy patients is between 16.8 and 58%. However, when considering only severe drooling, the reported prevalence is 15–33%. In these patients drooling decreases with age, which is related to maturation of orofacial neuromuscular system as the children grow older. In effect, in small children with primary dentition the prevalence of drooling is reportedly 75%, while in individuals with permanent dentition the figure drops to 43%.

In adult patients with neurodegenerative changes such as Parkinson's disease, the prevalence of daytime drooling has been estimated to vary between 20.8 and 28% [37].

1.5 Clinical assessment

1.5.1 History

The anamnesis is aimed at assessing the characteristics of sialorrhea, to identify its causes and therefore determine its correct management approach.

One of the first information to be obtained during history concerns the temporal pattern of sialorrhea: if a patient has symptoms throughout the day, then targeted therapies such as botulinum toxin and radiotherapy may need to include the submandibular gland, while if they have symptoms mainly when eating or drinking, treatment of the parotid glands may be more successful [19]. Discovering the real cause of drooling is essential to provide correct etiological treatment.

In the management of a patient with drooling it is important to obtain information on the impact of sialorrhea on the life of the patient and his family. The questions can be addressed both to the child himself and to the parents, to assess how much the disorder affects their lives and relationships with the child.

During the anamnesis, the clinician must focus on the therapy in progress and also on any anti-drooling treatments, to evaluate their effectiveness and any side effects. The importance of pharmacological history is linked to the fact that many drugs can cause sialorrhea as a side effect, especially through the induction of hypersalivation.

A complete and detailed medical history should include the following areas.

Age of onset The first step is to ask for the age of onset, which is useful both for diagnosis and for the etiological hypotheses of drooling. A mild degree of drooling has to be considered normal until 5-6 months of age. However, excessive drooling in the neonatal period (*congenital drooling*) should alert the physician to the possibility of esophageal atresia or withdrawal from maternal substance abuse. Sialorrhea after four years of age generally is considered to be pathologic [24].

Chronicity An acute onset suggests an acute disease, usually with different management and consequences in the patient's quality of life (i.e. infections or drug intoxications). Drooling of long duration may be developmental or secondary to a structural lesion, neuromuscular disorder, or mental retardation [24].

Severity Drooling quantification plays a key role in clinical assessment. Severe drooling can lead to social embarrassment and other several effects. The severity can be gauged by the frequency of bathing, wiping, and the need for bibs or clothing changes [24]. As shown in subsection 1.5.3, the subjective scales are the best method of evaluation.

Precipitating factors Any precipitating factors such as ingestion of food and teething should be noted [24].

Associated syntoms Fever, agitation, aphonia, dyspnea and stridor suggest epiglottitis [24]. Fever, sore throat, and dysphagia suggests peritonsillar abscess [24]. History of choking, gagging, coughing, vomiting, and dyspnea suggests a foreign body in the esophagus [24]. History of regurgitations, especially since the neonatal period, is suggestive of gastroesophageal reflux [24]. Lacrimation, sweating, headache, dizziness, and cramps suggest intoxication with organophosphates [24]. Feeding difficulties, excessive sweating, syncope, insensitivity to pain, slurred speech, and seizures are features of familial dysautonomia [24]. Developmental stagnation, altered communicative ability, loss of active play interaction, social withdrawal, stereotypic movements, periodic apnea, intermittent hyperventilation, constipation, weight loss, apparent insensitivity to pain, digit sucking or biting, and night-time laughing are features of Rett syndrome [24].

Developmental history A thorough developmental history is of extreme importance. Generalized delay in all aspects of developmental milestones suggests a psychomotor delay [24].

Drug use A detailed drug history is important because the use of medication such as haloperidol, pilocarpine, and diazepines may lead to drooling.

Psychosocial history Any psychosocial or emotional stress should be noted as a potential cause of the drooling. Besides, the impact of drooling on the child and family should be noted [24].

Perinatal history The perinatal history should include maternal illness during the pregnancy, gestational age at birth, birth weight, perinatal trauma, asphyxia, and infections [24].

Past history Significant illnesses such as cerebral palsy, facial nerve palsy, myasthenia gravis, and gastroesophageal reflux should be noted [24].

Family history A family history of a neurological disorder, such as Wilson disease, Rett syndrome or familial dysautonomia, suggests the corresponding disease [24].

1.5.2 Physical examination

The complexity of the patient suffering from drooling requires an adequate physical examination, focused on every aspect of the children. The physical examination consists of a general part, in which the clinician must evaluate the patient as a whole, and a more specific part, in which the clinician must evaluate above all the organs mainly involved in the pathogenesis of drooling. Besides, a very important aspect is represented by the evaluation of the conditions associated with drooling, which can lead to the correct diagnosis of the underlying pathology.

A brief description of the main components of the physical examination in a child with drooling or sialorrhea is reported below.

General examination The examiner should evaluate the weight, height, and head circumference of the child. Poor growth may be suggestive of a chronic disorder, such as Rett syndrome or intrauterine growth retardation (IUGR) [24]. Vital signs should be noted. If the patient has a fever, an underlying infection can be suspected as the cause of drooling. Intermittent hyperventilation is typical of Rett syndrome. Postural hypotension is suggestive of familial dysautonomia [24]. The patient's clothes should be inspected for wetness or staining. The examiner should pay particular attention to the oral health of the child: he should assess the presence of any oro-facial malformations and the health of the gums and teeth. A comprehensive developmental assessment should be done if mental retardation is suspected [24].

Associated signs examination The associated features may induce the clinician to suspect a specific basic etiology. If a certain syndrome is suspected, dysmorphic features should be noted. An infectious disease is associated with fever and other specific characteristics, such as trismus, inflammation of the tonsillar area, which suggest peritonsillar abscess. Toxicity, fever, respiratory distress with inspiratory stridor, flaring of the alae nasi and inspiratory retractions of the suprasternal notch suggest epiglottitis [24]. Cerebral palsy can be associated with spasticity, hyperreflexia, ankle clonus, extensor plantar response, dysarthria, athetosis, ataxia, and contractures. Inability to close the eye and drooling at the corner of the mouth point to facial nerve palsy [24]. Jaundice, dysarthria, clumsiness, tremor, gait disturbances and the presence of Kayser-Fleischer rings point to Wilson disease [24].

Clinical factors to be investigated
Clinical and social-emotional history
Motivation, physical, and cognitive ability to try to reduce sialorrhea
Use of medications (anticonvulsants, benzodiazepines, neuroleptics)
Neurological examination
Orofacial assessment
Oral hygiene, dental occlusion and health, labial sealing
Language and communication skills in general
Cognition
Respiratory health (hypersecretion, broncospasm, recurrent infections, atopy)
Presence of GERD
Presence and assessment of dysphagia
Nutrition

Table 1.12 Principal clinical features to evaluate in the assessment of children with drooling [10]. GERD, gastroesophageal reflux disease.

1.5.3 Drooling quantification and diagnostic tests

The management of a patient with drooling should include different laboratory and imaging tests, depending on the drooling etiology and physiopathology, and the clinical condition of the patient. Laboratory tests are ordered only when indicated by history or physical examination. For example, if an infectious disease is suspected it is useful to prescribe a complete blood count. Anteroposterior radiographs of the neck using a soft tissue technique are very useful for localizing a radioopaque foreign body, detecting the increased thickness of the prevertebral soft tissue, and confirming or ruling out a swollen epiglottis [24]. An upper gastrointestinal series may be considered to rule out the possibility of esophageal stricture or gastroesophageal reflux [24]. The *Denver Developmental Screening Test* should be performed if mental retardation is suspected. The *Standford-Binet Intelligence Scale*, the *Bayley Scales of Infant Development*, the *Wechsler Intelligence Scale for Children-Revised*, and the *Wechsler Preschool and Primary Scale of Intelligence* are the intelligence tests which should be used to assess the intellectual and adaptive functioning of a child [24].

It is difficult to measure sialorrhea. The child must not realize that he/she is being observed and should be assessed during everyday situations. Nevertheless, it is necessary to quantify

the frequency and severity of sialorrhea, as well as its impact on the quality of life of children and their caregivers. The severity and impact of sialorrhea can be evaluated through objective or subjective methods.

Objective methods

Objective methods are reported in Tab.1.13. They consist of the direct measurement of anterior sialorrhea [10]. The direct quantification of drooling is essential to evaluate the effects of different interventions and their development is still a challenge both in the research field and in clinical practice [10]. Nowadays, the major limitation of many studies on drooling is the absence of standardized quantitative methods to assess the effectiveness of the treatment [31].

The amount of drooled saliva has been quantified using scintigraphy with radioactive isotopes. However, this method was found invasive, cumbersome, and problematic.

Collection devices have also been used, such as suction bags used as collecting units for saliva. Sochaniwsky et al. introduced a cup-like collection device held against the chin with straps attached to the orthodontic head bonnet; the saliva collected is then suctioned from the cup into a calibrated test tube where it would be measured. However, the occurrence of leakages makes the measurements inaccurate. Other approaches that have been used include bib weighing and the use of absorbent cotton dental rolls inserted into the oral cavity. However, imprecisions have also been reported with these methods.

The Drooling Quotient (DQ), a semi-quantitative observational method, is a direct observational objective method that quantifies the number of drooling episodes occurring over two observation sessions. Due to the long period of evaluation, which is needed to obtain an accurate drooling score, this method is difficult to perform in patients with severe neuromuscular disease and patients with severe agitation [31]. Moreover, long stringy drools have a greater volume than small drips, and this measure does not reflect these differences in quantity [32].

Objective methods to measure sialorrhea		
Technique	**Method**	**Description**
Sochaniwskyi's technique	Saliva collection	Collection of saliva that reaches the chin using a glass for 30 minutes
Drooling Quotient (DQ)	Saliva collection	DQ{%}=100 x the number of episodes of sialorrhea/60 observations*
Salivary glands scintigraphy	The amount of drooled saliva is quantified using radioactive isotopes	
Others	Measuring the weight of the container used for direct collection of saliva	Use of collection units, towels, and diapers or dental cotton rolls

Table 1.13 Description of the objective techniques to measure sialorrhea. *At every 15 s, in a 15-minute period (60 observations) the presence or absence of sialorrhea is observed [11].

Subjective methods

Subjective scales represent the most appropriate method to evaluate and quantify sialorrhea impact on families, caregivers, and the patients themselves. Drooling consequences on a patient's quality of life is essential to assess the effectiveness of any treatment. A nominal scale is an important part of both pre-treatment and post-treatment assessment [43]. The definitive method for evaluating the effectiveness of any treatment for sialorrhea is one that measures how much the life of the caregiver has been facilitated and that quantifies the improvement in the child's quality of life. Subjective scales are filled out by patients or their caregivers, which express their qualitative and quantitative impressions of the severity and impact of sialorrhea. Some examples of these scales are reported in Tab. 1.14 [43].

Subjective methods to measure sialorrhea
Drooling Impact Scale (DIS)
Drooling Severity and Frequency Scale (DSFS)
modified Teachers' Drooling Scale (mTDS)

Table 1.14 Subjective scales used to evaluate severity, frequency, and consequences of drooling [43].

Drooling Impact Scale (DIS) The Drooling Impact Scale (DIS) is a subjective method of evaluating sialorrhea. It is a questionnaire consisting of 10 questions that address the patient's parent or caregiver. The topics of the questions are very varied, including both the simplest aspects of sialorrhea, such as its severity and frequency and its clinical and

psychological effects in the patient's life. Parents must score 1 to 10 for each question, following the *Numeric Rating Scale* (NRS). Fig 1.8 shows a version of the DIS scale, with the *Visual Analogue Scale* (VAS). The representation of the numerical scale in a straight line can help parents in interpreting the question. The total score ranges from 10 to 100. In literature, the DIS scale is described as an evaluative tool to assess the effect of saliva-control interventions on drooling in children with developmental disabilities. Susan M. Reid et al. [32], in "The Drooling Impact Scale: a measure of the impact of drooling in children with developmental disabilities", describe the development and clinimetric properties of this scale to evaluate changes in the impact of drooling in children with developmental disabilities. Their analyses support the usefulness of the Drooling Impact Scale as an evaluative tool to assess the effect of saliva-control interventions on drooling in children with developmental disabilities. The scale has been shown to behave as expected in validity studies, to have good test–retest reliability in stable children, and to be responsive to change in children who have undergone saliva-control interventions [32].

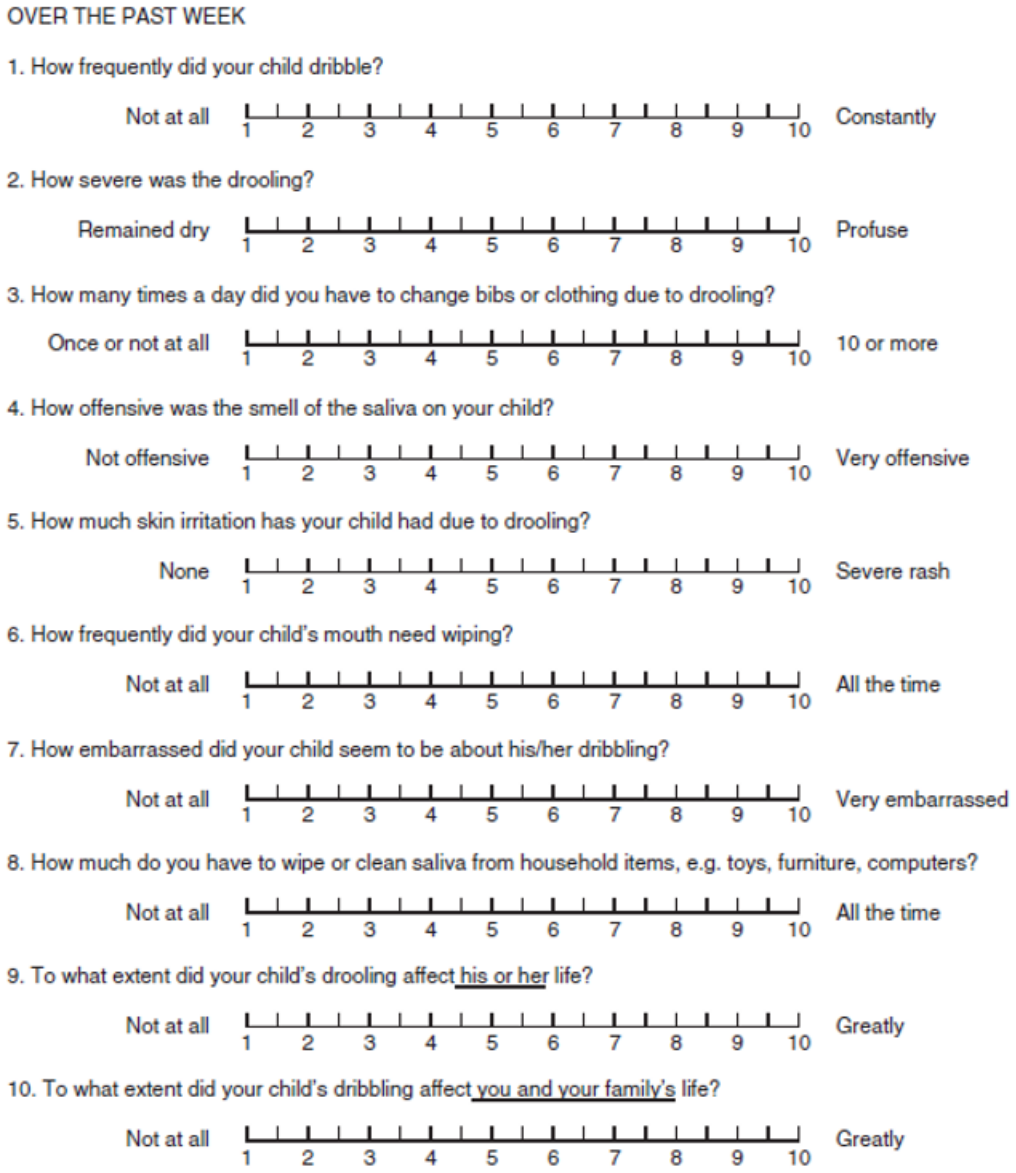


Fig. 1.8 The Drooling Impact Scale. From: Susan M. Reid et al., "The Drooling Impact Scale: a measure of the impact of drooling in children with developmental disabilities" [32].

Drooling Severity and Frequency Scale (DSFS) The Drooling Severity and Frequency Scale is a subjective method whereby parents are asked to rate the severity and frequency of drooling. The Drooling Score equals the sum of the Severity and Frequency sub-scores (Tab. 1.15). This scale is also called the "Drooling Rating Scale", Thomas-Stonell and Greenberg classification, which is useful for evaluating drooling severity and frequency. Score points can be assigned either by parents/caregivers or by the clinician, at the end of the physical examination. The total score ranges from 2 to 9.

Drooling Severity and Frequency Scale (DSFS)
Drooling Severity Scale 1 = Dry (never drools) 2 = Mild (wet lips only) 3 = Moderate (drool reaches the lips and chin) 4 = Severe (drool drips off chin and onto clothing) 5 = Profuse (drooling off the body and onto objects, such as furniture, books, etc.)
Drooling Frequency Scale 1 = No drooling 2 = Occasionally drools 3 = Frequently drools 4 = Constant drooling

Table 1.15 The Drooling Severity Scale and The Drooling Frequency scale.

Modified Teachers' Drooling Scale (mTDS) This scale is composed of a list of nine scores (Tab. 1.16), that represent the clinical condition of the patient. Parents or caregivers are asked to choose the score which best describes the clinical status of the children.

modified Teachers' Drooling Scale (mTDS)	
Score	*Description*
1	Dry: never drools
2	Mild: only the lips are wet; occasionally
3	Mild: only the lips are wet; frequently
4	Moderate: wet on the lips and chin; occasionally
5	Moderate: wet on the lips and chin; frequently
6	Severe: drools to the extent that clothing becomes damp; occasionally
7	Severe: drools to eh extent that clothing becomes dump; frequently
8	Profuse: clothes, hands, trays and objects become wet; occasionally
9	Profuse: clothes, hands, trays and objects become wet; frequently

Table 1.16 Modified Teachers' Drooling Scale (mTDS). Each score corresponds to the specific condition described on the right of the table.

Chapter 2

Treatments

2.1 Available Treatments

Just as drooling has many causes and predisposing factors, its management is best accomplished by using a team approach and many approaches to treatment have been employed. The conclusions reached in the available literature are often conflicting and rarely helpful in determining the best approach for the individual patient. The various methods that have been suggested are listed in Tab. 2.1 [19, 25].

Summary of treatment options
Conservative measures • Observation • Correction of situational factors • Speech and language therapy (oralmotor exercises) • Physiotheraphy • Behavior modification programs • Bio-feedback techniques • Bio-functional appliances
Drug therapy
Botulinum toxin injection
Radiotherapy
Surgical methods

Table 2.1 Different treatment approaches in drooling management. The first choice is represented by conservative measures and their failure is followed by drug therapy. Botulinum toxin injection, radiotherapy, and surgical methods are the third choice options, which are considered in case of failure of conservative or drug measures [19].

Children with sialorrhea should be assessed by a list of figures, who work in a team to best manage drooling manifestations and clinical effects. The primary care physician usually focuses on the complete history and physical examination of the patient, with special attention to the impact of drooling on quality of life and the potential for improvement. Speech pathologists and occupational therapists work with patients to improve their swallowing mechanics and to support their posture with devices such as the head back wheelchair. Dentists and orthodontists assess and treat dental and oral diseases and malocclusion. Otolaryngologists identify and correct causes of aerodigestive obstruction like macroglossia and adenotonsillar hypertrophy that contribute to drooling. Neurologists, otolaryngologists, and primary care physicians can assess the patient for significant cranial neuropathies. After a thorough assessment, a consensus on appropriate treatment options should be developed by the treatment team, the patient, and the patient's family. Treatments can be offered in a stepwise fashion, from least invasive, nonsurgical therapies to most invasive, as reported in Tab. 2.1 [19].

2.1.1 Conservative measures

Conservative measures are based on the concept of reducing drooling in a non-invasive way, acting on worsening factors. Several factors can contribute to the pathogenesis of drooling and this type of treatment aims at modifying the associated factors to improve the general condition of the patient. Since these measures are the least invasive, they are considered to be the first choice approach, especially in very young patients and with a slight degree of drooling. The aim is to decrease the symptom without causing particular side effects on the general state of the patient. Despite being less invasive, these treatment methods nevertheless require important participation from the child and his family.

Neck collars and head-back wheelchairs are useful devices to improve positioning and counteract a flexed posture. This simple measure is likely to improve patients' comfort and self-image. Oral prostheses, trialed in neurologically impaired patients to improve lip seal, improve quality of life. Portable suction devices can be considered in patients with treatment-resistant symptoms, particularly if they have pooling of saliva in the throat. While these devices are portable they are not necessarily discrete and patients may find using them embarrassing [25]. Adenotonsillectomy should be performed when indicated and dental malocclusion and caries should be treated. Several orthodontic appliances may be used for the treatment of sialorrhea. Customized plates formed to fit the palate can aid in better lip closure. Movable beads can be placed on the upper plate; they stimulate tongue movement, thus helping to deflect saliva toward the pharynx. The use of these beads in combination with swallowing therapy has been successful in patients with moderate sialorrhea [27]. The

following paragraphs provide a brief description of the main conservative measures used in the management of a patient with drooling.

Speech and language therapy Speech therapy should be involved early, aiming to maximize the patient's swallowing function and lip deal [19].

Behavioral therapy, physiotherapy, bio-functional therapy and bio-feedback techniques The first approach of treating sialorrhea is making the children aware that they drool by using the *anti-drooling classes*. The anti-drooling classes may be associated with *chin-cup* orthopedic appliances, which apply pressure on the chin to encourage the patients to achieve an anterior oral seal [22]. Children awareness of drooling may be obtained by using various means, such as using mirrors as visual reminders, playfully teaching them to establish anterior lip seal (by pronouncing *"mmm"* sounds) and encouraging them to develop an automatic response to the command "suck and swallow" with the help of a physiotherapist [22]. It was reported that over a year period there was a 73% reduction in the volume of saliva drooled [22].

Bio-functional therapy is based on the improvement and stimulation of children's oral-motor activity and control. It has been successfully used in the management of drooling, chewing, and swallowing dysfunctions in children with cerebral palsy [22]. Different functional appliances have been used, such as a mouth vestibular brace or a stimulating plate to stimulate lip function, but their efficacy is almost unknown. In many cases maintaining the head in an upright position and substituting the lost reflex by willpower controlled swallowing successfully improved orofacial motor control. Other methods, such as stimulating or brushing the oral soft tissues in a certain pattern in conjunction with *chin vibration therapy*, have been shown to be unhelpful. Feeding programs with the overall aim of developing the patient's oral skills such as sucking, lip closure, tongue, and jaw movements have been tried, but with little success [22].

Biofeedback techniques are aimed at rendering swallowing as a conscious act, by linking the swallowing reflex with a regular auditory stimulus. These methods seemed most useful in children of normal intelligence and high motivation and have successfully treated patients with mild neurologic dysfunction and drooling. Patients are trained to associate a behavior with a cue; for example, swallowing or wiping the face is associated with an electronic beep. These devices can be used for several hours a day. The drawback to these devices is that patients become habituated to the stimulus, and the devices become less effective after repetitive use [22, 19].

2.1.2 Non-invasive and invasive methods

Medication, radiation and surgical therapy should be considered if sialorrhea continues to interfere with the patient's health and quality of life after conservative measures have been tried [19].

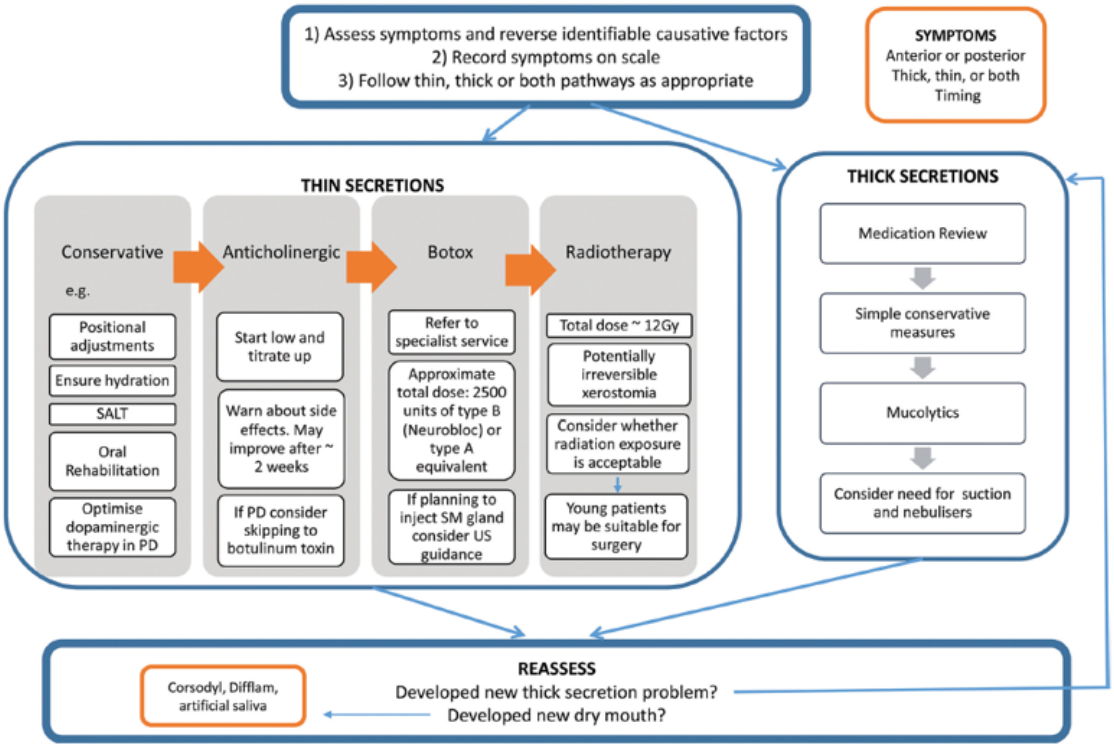


Fig. 2.1 Alexander J. McGeachan et al. [25] suggest a generic management approach to a patient with symptoms relating to oral secretions. This flowchart distinguishes between thin and thick secretions and describes how to manage the patient correctly in every step of the treatment [25]. PD, Parkinson's disease; SM, submandibular; US, ultrasound.

Drug therapy Salivation is mediated through the autonomic nervous system primarily by the way of the cholinergic system's muscarinic receptor sites. The blockade of these receptors inhibits nervous stimulation to the salivary glands [40]. Many drugs cause xerostomia as a side-effect, principally atropinics, monoamine oxidase inhibitors, and tricyclics [22]. Antimuscarinic drugs (e.g. atropine) can be used to decrease drooling, but unfortunately, they have widespread effects at all end organs that are governed by muscarinic stimulation, and there is little selectivity in terms of blocking transmission at only the desired site. Variations in the structure of natural and synthetic compounds result in somewhat different quantitative actions at different organs. For example, central stimulation consisting of restlessness,

irritability, and even delirium are side-effects of atropine, whereas mild sedation is more commonly produced by scopolamine. Known physiologic effects of anticholinergic agents are reported in Tab. 2.2; they can be considered as both pharmacological and side effects [40].

Effects of muscarinic blockade
CNS: stimulation/depression
Eyes: pupillary dilation (photophobia) and cycloplegia (blurred vision); decreased tearing
Ear, nose and throat: decreased secretion (dry nose), decreased vestibular response
Salivary glands: decreased secretion (xerostomia)
Bronchi: small airway dilatation
Heart: tachycardia
Stomach and bowel: decreased secretion; decreased motility (constipation)
Bladder: decreased detrusor muscle tone (diminished/delayed emptying)
Skin: decreased sweating (increased temperature, flushing)
Muscle: decreased tone, decreased adventitious movement

Table 2.2 Physiological consequences of antimuscarinic activity. CNS, central nervous system [40].

A large number of drugs have been tried to diminish drooling, but no one drug is perfectly selective, so the use of antimuscarinic carries a price in terms of side-effects (Tab. 2.3). The prevalence of side-effects is related not only to the type of molecule involved but also to its dose and route of administration. However, a common characteristic of these agents is their tendency to be most effective where excessive parasympathetic stimulation is at the root of the problem. In other words, pharmacotherapy is most likely to be effective where salivation is excessive, a situation believed to be uncommon in the CP and other neurological disorders population. There are various anticholinergics and drugs with anticholinergic effects that are used to manage sialorrhoea, including hyoscine hydrobromide, atropine, glycopyrrolate, tropicaimide, hyoscyamine sulfate, and the tricyclic antidepressant amitriptyline (Tab. 2.3) [25].

Examples of anticholinergic drugs used to treat sialorrhea			
Name	*Preparation*	*Dose*	*Characteristics*
Hyoscine Hydrobromide	Transdermal patch	0.5mg patch for 72h	Skin reaction at the site of the patch (alterning the site and using topical steroid)
Glycopyrronium	Tablet Oral solution	1-2mg t.i.d.	Less frequent CNS side effects (the quaternary ammonium structure is less permeable to the blood--brain barrier)
Amitriptyline	Tablet	10-50mg q.h.s.	More frequent CNS effects (sedative, antidepressant) but not at antisialogogue dose
Atropine	0.5% Eye drops	1-2 drops S.L. q.4-6h	Useful in sialorrhea related to meals
Scopolamine (Transderm Scop)	Trasdermal patch	1.5 mg q.d.	Minimal side effects with short term use (pruritus, urinary retention, irritability, blurred vision, dizziness, glaucoma)
Benzotropine Mesylate	Oral		Blurred vision, dryness of mouth, constipation
Benzhexol Hydrocloride			
Trihexyphenidyl Hydrochloride			

Table 2.3 Antimuscarinic drugs used in sialorrhea treatment: molecule, dosage and side effects [25]. h, hours; t.i.d., three times a day; q.h.s., before bed; S.L., sublingually; q.4-6h, every four-six hours; q.d., once a day; CNS, central nervous system.

Scopolamine is by far the most important of the anti-drooling agents. It is usually administered by a transdermal patch, but another option is represented by the nebulized formulation. Scopolamine transdermal patch is commonly used to prevent nausea and vomiting associated with motion sickness. Dry mouth, which is the most common side-effect

of this drug, has been used advantageously in the treatment of patients with drooling. The efficacy of transdermal scopolamine is said to be variable across patient populations and treatment approaches must be individualized. Although these patches have been used in children, the manufacturers do not recommend their use in children under 10 years due to the relative lack of clinical experience [22].

Another drug substance that has been used is glycopyrrolate, which has a quaternary ammonium structure similar to that of atropine, with antimuscarinic effects. It has been one of the most widely used drugs for the treatment of drooling [37]. The recommended dose is 40 to 100 µg/kg per day to be given once or twice daily. To obtain optimal results, the dosage should be adjusted to the individual patient's response. The drug is long-acting, does not cross the blood-brain barrier, and has minimal side effects. Glycopyrrolate is five to six times more potent than atropine in its antisialogogue effect. However, it causes dry mouth, urinary retention, constipation, and behavioral changes such as irritability [24].

Other pharmacological agents that have been used in the treatment of drooling include benzhexol hydrochloride/benztropine which are synthetic drugs with antimuscarinic effects that can improve drooling control [22, 37].

Finally, the usage of atropine sulfate as an anti-drooling agent has been anecdotally reported. Sublingual atropine reduces drooling, but this treatment is contraindicated in patients with cognitive problems, as in dementia, and patients with psychotic symptoms (psychosis has been described due to atropine poisoning) [22, 37].

Botulinum toxin injection Botulinum toxin is a neurotoxin produced by the bacterium Clostridium botulin, which inhibits the release of acetylcholine from the cholinergic nerve ending [37, 25]. There are seven types of botulinum toxins (A-G), that works by penetrating the axon terminals and degrading synaptosome associated protein (SNAP)-25 proteins, preventing neurosecretory vesicles fusion with the nerve synapse plasma membrane [25]. These toxins have been used since the 1980s to treat conditions such as strabismus and dystonia [25]. Both botulinum toxin A and B have been used to manage sialorrhea, but toxin A is one of the most widely accepted treatment options, especially in children with cerebral palsy [37, 25]. The toxin is injected percutaneously into the parotid and submandibular glands under ultrasound guidance improve the efficacy and safety of the technique. Two to three sites are usually injected in the parotid gland, together with 1–3 sites in the submandibular glands. In children, it can be administered under general anesthesia [37]. The effect lasts for between 6 weeks and 6 months [37]. Approximately 10% oh the patients fail to respond to this treatment. Local side effects are represented by bruising, carotid artery or facial nerve damage, and chewing or swallowing problems caused by the action of the toxin upon the

masticatory or pharyngeal muscles (31). In Tab. 2.4, Alexander J. McGeachan et al. [25] described the different effects of toxins A and B on drooling management.

Botulinum toxin for the management of sialorrhea
Type A • *Botox* and *Dysport* are the subtypes of botulinum toxin A used to treat sialorrhea Type B (*NeuroBloc*) • Higher risk of anti-drugs antibodies production
Dosing • 100 MU of Botox, 250 MU of Dysport, 2500 MU of NeuroBloc • The total dose is divided between submandibular and parotid glands (a greater dose for parotids)
Delivery US guidance (more accurated) Landmark guided (practical and safe)
Advantages • Meta-analysis data supporting its clinical efficacy • Effective in patients with symptoms resistant to medications • Effects last for 3–6 months • Fewer side effects than anticholinergic medication • Minimally invasive • May decrease risk of aspiration pneumonia Disadvantages • Common adverse effects: xerostomia, thickened bronchial secretions and viscous saliva, difficulty chewing and pain at the site of injection • Disphagia is a rare side effect • Antibodies formation and failure
Group characteristics • Patients with motor neuron disease are at higher risk of side effects • Old age is associated with longer benefit duration

Table 2.4 Botulinum toxin injections and their safety and efficacy in drooling treatment [25]. US, ultrasound.

Radiotherapy External beam radiotherapy using photons or electrons is usually used as a third option treatment in patients with drooling that failed to respond to or tolerate treatment with anticholinergic drugs and botulinum toxin [25]. Radiotherapy can significantly reduce saliva production and improve patient symptoms, as reported in several retrospective and

prospective studies. While these studies did not include control groups, the same patients had previously failed to achieve symptom control with other available treatments for sialorrhea [25]. Most commonly used regimens target both submandibular glands and the caudal two-thirds of both parotid glands, with a median dose per fraction of 5 Gy (0.83–8 Gy) and a mean total dose of 12 Gy (3–48 Gy). The length of the effect of radiotherapy is variable and last for several months to 5 years. Radiotoxicity can occur resulting in an overly dry mouth with more viscous saliva, facial erythema, pain, and nausea. Because many of the patients with a neurological disease have a short life expectancy, there is less concern about malignancy; however, in those with longer life expectancy, this may be an unnecessary risk [25].

Surgical methods The surgical approach in sialorrhea management is commonly used in neurologically impaired children with severe symptoms resistant to medication and botulinum toxin [22, 25]. These interventions are usually not indicated in older patients, because of the invasive procedures and the short life expectancy of these patients [25]. Numerous techniques have been proposed but the most successful techniques fall into the following categories: (a) Procedures that attempt to reduce the total amount of saliva produced by sectioning the parasympathetic nerve supply to the salivary gland, excising the salivary gland, or ligating the salivary ducts. (b) Procedures that aim at redirecting the salivary flow by rerouting or relocating the salivary duct. (c) Procedures that combine both the above options [22]. The most widely used techniques are those that cause fewer side effects, and surgical therapy aims at minimizing drooling while specifically avoiding the complications of xerostomia [22, 37]. As a result, any surgical method must allow for a sufficient remaining volume of salivary flow [22]. However, many patients with motor neuron disease, Parkinson's disease, and other neuromuscular and neurodegenerative disorders do not have the functional reserve to tolerate surgical intervention [25].

a. *The sectioning of the parasympathetic neural pathway.* The section can be carried out at any point in the pathway, but the preferred sectioning procedures are the *transtympanic chorda tympani and tympanic sectioning procedures*, either uni- or bilaterally, and either alone or in combination with another procedure such as excision of one submandibular gland [22]. Despite high success rates, the recurrence of drooling in the long term has been reported [22]. Another option is represented by the *tympanic neurectomy*, which is carried out via the external auditory canal, where the tympanic membrane is elevated, and the nerves of the tympanic plexus are divided [22]. There is a very small risk of hearing loss. The success rate varies between 74% and 87% [22]. *Sectioning of the chorda tympani nerve* is performed at the point where the nerve runs

through the middle ear to reduce salivary flow from the sublingual and submandibular glands [22]. The inevitable side effect is the loss of taste sensation in the anterior two-thirds of the tongue [22].

b. *Relocation/ligation of salivary duct(s) with or without excision of the salivary gland(s).* The transposition of the parotid ducts is pioneered by Wilkie and is known as the Wilkie's procedure. It consists of *bilateral parotid duct retropositioning and bilateral submandibular gland removal* [22]. The opening of the parotid duct (normally opposite the second maxillary permanent molar) is repositioned via an intra-oral approach to allow salivary flow to emerge behind the tonsillar pillar [22]. This operation was successful in reducing drooling with a success rate up to 89% but was associated with a wide array of complications including wound dehiscence, duct stenosis, septic parotitis, and gingivitis [22]. *Ligation of the salivary ducts* is considered the only technique that leads to a consistent reduction in drooling, especially when combined with submandibular gland excision. Complications are represented by chronic sialadenitis and transient orofacial swellings [22].

2.1.3 Clinical trials

Tab. 2.5 reports eight clinical trials that evaluate the use of anticholinergic agents for the treatment of drooling in neurological impaired children. These studies aim at measuring antimuscarinic drugs effectiveness and safety in reducing drooling. Most of these clinical trials use glycopyrrolate and evaluate its action against placebo or other anticholinergic agents that were previously used in sialorrhea management.

Studies of anticholinergics for drooling treatment						
Authors, Year, [Ref]	**Sample size**	**Age range**	**Study population**	**Drugs**	**End points**	**Conclusions**
Susan M. Reid et al., 2019, [2]	110	1y 11 mo 18y 11mo	Children with drooling and developmental disability (CP, ID, ASD)	Benzhexol vs. Glycopyrrolate vs. Scopolamine	Effectiveness in reducing drooling; frequency and nature of side effects	Meaningful reduction in drooling offset by side effects; Glycopyrrolate performs best
Jeremy R. Parr et al., 2017, [7]	90	35mo 16y	Children with drooling and neurodisability who had never received medications for drooling	Hyoscine 1 patch/3d vs. Glycopyrrolate oral solution 100mcg/kgx3 fro 12w	Effectiveness and acceptability to treat drooling	Hyoscine and Glycopyrrolate are clinically effective in treating drooling. Hyoscine produced more problematic side effects
Robert S. Zeller et al., 2012, [24]	137	3y 18y	Children with moderate-to-severe drooling associated with CP and other neurological conditions	Glycopyrrolate oral solution 1mg/5mL for 24w	Safety and efficacy in reducing drooling	Glycopyrrolate substantially reduced the percentage of patients with moderate-to-severe drooling
Robert S. Zeller et al., 2012, [26]	38	3y 16y	Children with severe drooling associated with CP and other neurological conditions	Glycopyrrolate oral solution 1mg/5mL for 24w vs. placebo	Efficacy in reducing drooling	Significantly better response, as assessed by mTDS, to Glycopyrrolate than to placebo
Richard J. Mier et al., 2000, [168]	39	4y 4mo 19y	Children with severe sialorrhea and neurodevelopmental conditions	Glycopyrrolate oral solution 0.1mg/kgx3 for 8w vs. placebo	Efficacy and safety in reducing drooling	Glycopyrrolate is effective in the control of sialorrhea; 20% of children experienced substabtial adverse effects
Steven J. Bachrah et al., 1998, [125]	41		Children with drooling and developmental disability (CP, ID) or specific diagnoses (Moebius syndrome, fetal alcohol syndrome, Aicardi syndrome, Fahr disease, glutaric aciduria)	Glycopyrrolate 0.01-0.14mgx3 vs. Benztropine vs. Scopolamine patch	Efficacy and safety in reducing drooling	Improvement in drooling occurred in 95% of cases; side effects (dry mouth, thick secretions, urinary retention, flushing) in 44% of cases but discontinuation of pharmacologic in less than a third
L.M. Stern et al, 1997 [70]	24	3y 23y	Children and young adults with moderate-to-profuse drooling and disabilities	Glycopyrrolate 40-175mcg/kg for 5w-28mo	Efficacy in reducing drooling	Glycopyrrolate is effective and well-tolerated
Peter A. Blasco et al., 1996, [132]	40	4y 27y	Children and young adults with severe or profuse drooling and neurological disabilities (CP, RTT, spinal cord injury)	Glycopyrrolate 0.01-0.82 mg/kg for 8mo-4y	Efficacy and safety in reducing drooling	Glycopyrrolate therapy safely and effectively decreased but rarely abolished drooling

Table 2.5 Glycopyrrolate compared to other commonly used anticholinergic drugs. CP, cerebral palsy; ID, intellectual disability; ASD, autism spectrum disorder; vs., versus; y, years; mo, months; w, weeks; RTT, Rett syndrome.

As reported in Tab. 2.5, the earliest clinical trial is conducted by Peter A. Blasco et al. in 1996 [3]. They performed a prospective, open-label study of drug dosage parameters, response to therapy, and side effects, in 40 patients (age range, 4-27y, mean age, 12y 6mo). These children and young adults were recruited from the Cerebral Palsy Outpatient Clinic of Gillette Children's Hospital, St Paul, Minn, and were affected by a neurological disorder with a severe or profuse degree of drooling. In particular, thirty-six patients had cerebral palsy, 2 had Rett syndrome, 1 had a high spinal cord injury, and 1 did not have a specific motor diagnosis (she had severe mental retardation) [3].

In an unblinded fashion, all patients were prescribed glycopyrrolate, starting at a dose of 0.5 mg once or twice daily. Patient responses and side effects were initially monitored by telephone every 5 to 10 days to establish the effective dose clinically and to monitor for benefits and side effects. Response to therapy was based on the subjective reports of parents, other caretakers, or both, relying primarily on the question: "Is the drooling worse, better, or the same?". Follow-up has ranged from 8 months to 4 years [3].

Two patients immediately developed an allergic reaction to the drug and left the study. The 95% of the remnant patients (36/38) reported that their drooling had improved, but it was not completely abolished [3].

Fig. 2.2 [3] shows the principal side effects detected and studied in the 36 patients who responded to the treatment with glycopyrrolate. The most common side effects are represented by personality changes, especially irritability (4 patients), and constipation (3). Overall, 12 (30%) of the 40 patients discontinued treatment: 1 because of personal preference, 2 because of lack of benefit, and 9 because of unacceptable side effects, including the 2 with allergic reactions [3].

Side Effects of Glycopyrrolate Therapy in 40 Patients

Side Effect	No. Reported	No. Leading to Discontinuation
Irritability	4	3
Constipation	3	1
Hives	2	2
Urinary retention	1	1
Dry mouth and epistaxis	1	1
Skin flushing and irritability	1	1
Headache	1	0
None	27	0

Fig. 2.2 The list of side effects reported in patients who received glycopyrrolate. From: Peter A. Blasco et al., "Glycopyrrolate Treatment of Chronic Drooling" [3].

In conclusion, Blasco et al. [3] demonstrated glycopyrrolate safety and efficacy in drooling treatment, describing its principal side effects.

In 1997, L.M. Stern et al. [39] performed a "Preliminary study of glycopyrrolate in the management of drooling". They recruited 24 children and young adults (range 3-23y) with moderate to profuse drooling and disabilities and prescribed them glycopyrrolate at the dose of 40-1 00 µg/kg per day with a maximum of 175 µg/kg per day [39]. The lower dose was used to initiate therapy and the dosage increased until a significant decrease or cessation of drooling occurred. The dosage was given once daily early in the morning as absorption of glycopyrrolate from the gastrointestinal tract is slow. Duration of therapy varied from 5 weeks to 28 months [39]. Some time after the end of the trial parents were asked to complete a questionnaire to assess the effect of glycopyrrolate [39].

The majority of subjects showed improvement in both severity and frequency of drooling while taking glycopyrrolate. The results, analysed using *Wilcoxon signed rank analysis*, were highly significant (for severity $p = 0.0003$; for frequency $p = 0.0068$).

In conclusion, Stern et al. [15] reported glycopyrrolate acceptability and efficacy in drooling management, because of its specific antisialogogue action and lesser incidence of side-effects, compared to other anticholinergic agents.

In “Use of Glycopyrrolate and Other Anticholinergic Medications for Sialorrhea in Children with Cerebral Palsy”, Steven J. Bachrach et al. [1] evaluated the differences between glycopyrrolate, benztropine and scopolamine patch in children with drooling and a neurological disorder. The study was conducted in 54 patients, with specific characteristics: thirty-five of 41 patients had cerebral palsy (31 spastic, two hypotonic, and two athetoid, with nearly all the patients having spastic quadriplegia), one had mental retardation without significant motor impairment, and five had specific diagnoses (Moebius syndrome, fetal alcohol syndrome, Aicardi syndrome, Fahr disease, and glutaric aciduria) associated with motor impairments (mostly spasticity) [1].

Of the 41 patients, 37 received glycopyrrolate, three benztropine, and one scopolamine patch. For the 37 patients receiving glycopyrrolate, the mean dose was 0.051 mg/kg/dose, with a range of 0.01 to 0.14 mg/kg/dose, most commonly given three times a day [1]. In order to evaluate the pharmacological response, families or caregivers were given a questionnaire or interrogated by telephone calls.

On a five-point rating scale (with 1 being no drooling and 5 being severe drooling), 37 of 39 patients who completed the questionnaire reported improvement and two reported neither improvement nor worsening. The differences between the pretreatment and posttreatment scores were analyzed by the use of the *Wilcoxon Matched Pairs Signed Ranks Test*. The mean pretreatment score for all subjects was 4.59, whereas the posttreatment score was 2.41 ($p < 0.01$ on the Wilcoxon Matching Pairs Signed Ranks Test) [1]. The most commonly reported side effects were dry mouth and/or thick secretions in seven (19%), urinary retention in seven (19%), flushing in four (11%), constipation in two, pseudo-obstruction in one, and agitation and personality change in one [1].

In 2000, Richard J. Mier et al. [26] conducted another study to determine the safety and efficacy of glycopyrrolate in the treatment of developmentally disabled children with sialorrhea. This placebo-controlled, double-blind, crossover dose-ranging study involved thirty-nine children (range 4y 4mo-19y) from two different pediatric hospitals, with both developmental disabilities and severe sialorrhea [26]. The primary outcome was parent and investigator evaluation of change in sialorrhea and adverse effects.

Patients were administered an oral dose of glycopyrrolate with a specific timing pattern. After an initial physical evaluation and a 1-week baseline medication-free observation period, each child was assigned randomly to either the drug or placebo treatment arm, each of which

was 8 weeks long. At the end of the first arm, there was a 1-week washout period and a second week-long observation period, followed by the reciprocal arm, also 8 weeks in length [26]. Drooling was scored on mTDS scale, which ranged from 1 (never drools) to 9 (clothing, hands, and objects frequently become wet). Thirty-four children had cerebral palsy; 1 each had Smith-Lemli-Opitz syndrome, closed head injury, partial trisomy 22, congenital toxoplasmosis, and spinal muscular atrophy. Eleven children had additional medical conditions, most commonly a seizure disorder (6 children) but also including autism, fetal alcohol syndrome, hydrocephalus, congenital heart disease, hypothyroidism, and retinitis pigmentosum [26]. Two dosage regimens were used based on the weight category of the child: children weighing less than 30 kg began at 0.6 mg, increasing weekly to 1.2 mg, 1.8 mg, and 2.4 mg. Children weighing more than 30 kg began by taking 1.2 mg, increasing weekly to 1.8 mg, 2.4 mg, and 3.0 mg [26].

All 27 children who completed the study demonstrated improvement in drooling (Fig. 2.3). The mean baseline drooling score improved with glycopyrrolate from 7.52 to a maximum mean score of 1.85. A mean score of 1.85 corresponds to a description between "dry, never drools" and "mild drooling; only the lips are wet occasionally." With placebo, the baseline score improved slightly from 7.44 to 6.33. Mean drooling score on glycopyrrolate (1.85) compared with placebo (6.33) is statistically different, with $p < 0.001$ [26]. Drooling scores improved with increasing doses in a linear manner [26]. In this study, Mier demonstrated glycopyrrolate effectiveness and described its side effects (Fig. 2.6), experienced by approximately 20% of children treated with this medication.

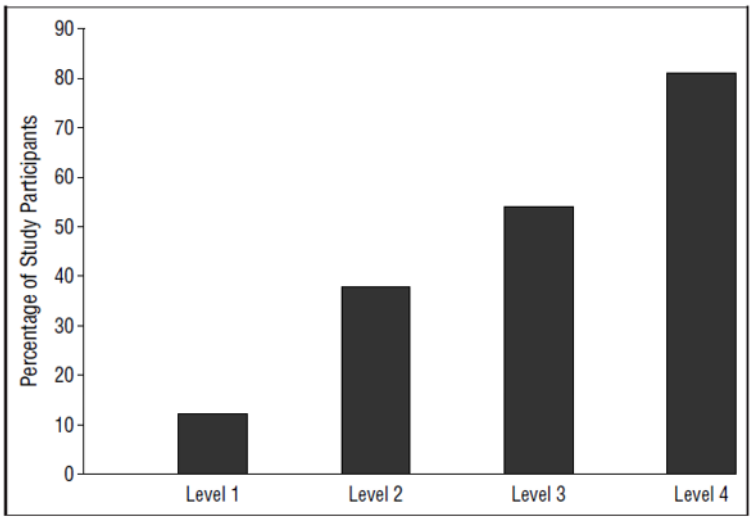


Fig. 2.3 Percentage of study participants who improved drooling score by 4 point or more at each dosage level, as reported in Mier's study [26]. From: Richard J. Mier et al., "Treatment of sialorrhea with glycopyrrolate" [26].

List of adverse effects reported by parents/caregivers on a weekly basis
Drowsy
Restless, overactive, or short attention span
Easily frustrated, irritable
Rapid mood changes
Explosive behaviour
Overly sensitive, serious, sad
Fearful
Worsening of coordination
Facial flushing
Nasal congestion
Excessively dry mouth
Vomiting
Constipation
Diarrhoea
Difficulty emptying bladder

Table 2.6 Reported side effects of glycopyrrolate in Mier's study [26]. From: Richard J. Mier et al., "Treatment of sialorrhea with glycopyrrolate" [26].

Glycopyrrolate was compared to hyoscine patch in a multicentre, single-blind, randomized controlled trial, performed by Jeremy R. Parr et al. in 2017 [30]. This study aims

at investigating whether hyoscine patch or glycopyrronium liquid is more effective and acceptable to treat drooling in children with neurodisability [30].

The trial population consists of ninety children with a neurological impairment who had never received medication for drooling (55 boys, 35 girls; median age 4 years) [30]. They are recruited from 15 UK National Health Service neurodevelopmental over 17 months. Children received hyoscine patches or glycopyrronium liquid according to an escalation protocol. Children randomized to hyoscine received the following regime: week-1: ¼ patch; week-2: ½ patch; week-3: ¾ patch; week-4: full patch [30]. The patch was replaced every 3 days and the site of the application is alternated, in order to minimize local skin reaction risk. Children randomised to glycopyrronium liquid received three doses per day: week-1: 40 μg/kg/per dose; week-2: 60 μg/kg/per dose; week-3: 80 μg/kg/per dose; week-4: 100 μg/kg/per dose to a maximum 2 mg per dose [30].

Primary outcome was Drooling Impact Scale (DIS) score at week-4. Secondary outcomes were change in DIS scores over 12 weeks, Drooling Severity and Frequency Scale and Treatment Satisfaction Questionnaire for Medication, adverse events, and children's perception of treatment. Both medications yielded clinically and statistically significant reductions in mean DIS at week-4 (25.0 (S.D. 22.2) for hyoscine and 26.6 (S.D. 16) for glycopyrronium) [30]. There was no significant difference in change in DIS scores between treatment groups. By week-12, 26/47 (55%) children starting treatment were receiving hyoscine compared with 31/38 (82%) on glycopyrronium [30]. There was a 42% increased chance of being on treatment at week-12 for children randomized to glycopyrronium relative to hyoscine (Fig. 2.4) [30].

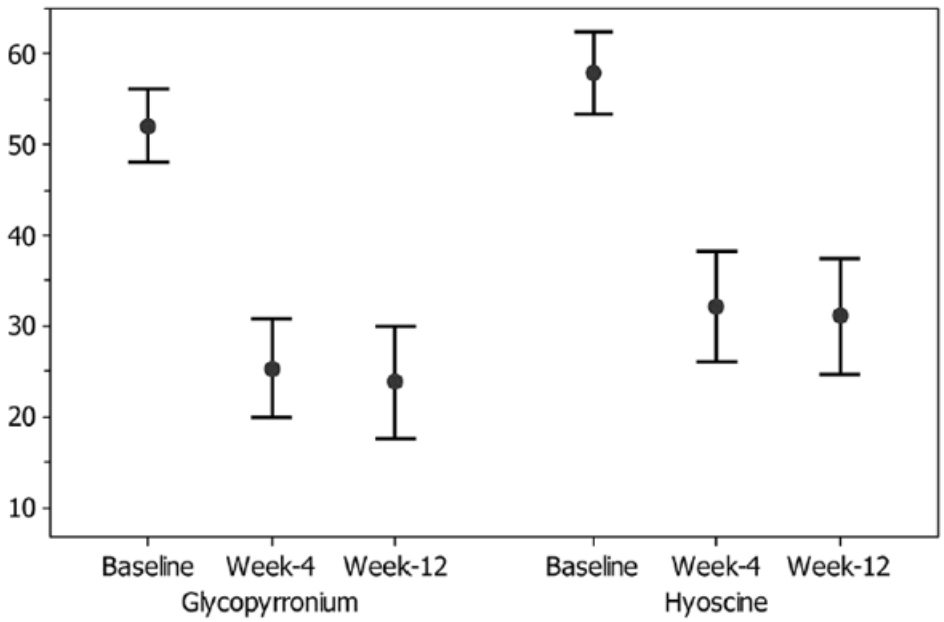


Fig. 2.4 Mean Drooling Impact Scale scores at baseline, week-4 and week-12 for the intention-to-treat group (with 95% CI), as reported in Parr's study [30]. From: Jeremy R. Parr et al., "Drooling Reduction Intervention randomised trial (DRI): comparing the efficacy and acceptability of hyoscine patches and glycopyrronium liquid on drooling in children with neurodisability" [30].

While hyoscine patches were well tolerated by some children, almost half of parents stopped medication (21/47, 45%), significantly higher than for glycopyrronium which was associated with fewer problematic side effects and was better-tolerated [30]. These results indicate that neither medication is contraindicated or definitely preferred, but glycopyrronium should be the drug of the first choice.

In 2012, Robert S. Zeller et al. published another study to assess the safety and efficacy of glycopyrrolate in the management of patients with drooling [44]. They enrolled 137 males and females (range of age 3-18y) who presented moderate-to-severe drooling (defined as score ≥ 5 on mTDS) associated with a neurological condition, such as cerebral palsy and mental retardation. The treatment period was 24 weeks, with scheduled visits on day 1 and at weeks 4, 8, 12, 16, 20, and 24 [44]. Oral glycopyrrolate solution 1 mg/5 mL was titrated over 4 weeks in each patient. The starting dose was 0.02 mg/kg three times daily, followed by increments of 0.02 mg/kg every 5–7 days for 4 weeks to an optimal maintenance dose or a maximum dose of 0.1 mg/kg, but not exceeding 3 mg three times daily [44]. The optimal dose was defined as the dose at which a patient received the maximum benefit from the study drug (greatest improvement in drooling) while experiencing minimum side effects [44].

Safety was assessed by physical examination and using the *modified Behavioral and Medical Rating Scale* (mBMRS), which was completed by the parent/caregiver twice weekly (every 3–4 days) from the first dose of study drug until week 4. The mBMRS includes 28 predefined symptoms, each rated on a four-point scale, i.e., 1 = not at all, 2 = just a little, 3 = quite a bit, and 4 = very much (Tab. 2.7).The primary efficacy endpoint was change from baseline to week 24 on the mTDS, as determined by the parent/caregiver. Patients showing at least a three-point decrease on the mTDS were defined as responders [44].

The modified Behavioral and Medical Rating Scale (mBMRS)	
Behavioral	*Physiological*
Restless/overactive	Fearful
Excitable/impulsive	Diarrhoea
Disturbs other children	Constipation
Fails to finish things	Drowsy
Costantly fidgeting	Nasal congestion
Inattentive/easily frustrated	Vomiting
Cries often and easily	Irritable
Mood changes quickly and drastically	Dry mouth
Temper outbrusts	Difficulty urinating
Overly serious, sensitive, sad	Flushing of skin
Change in coordination and/or body control	Headache
	Blurred vision
	Heart palpitations
	Increased heart rate
	Skin rash
	Skin hives

Table 2.7 The prespecified symptoms in the modified Behavioral and Medical Rating Scale (mBMRS) [44].

Most patients (n. 122; 89%) had at least one treatment-emergent adverse event with mild-to-moderate intensity. The most commonly reported treatment-emergent adverse events are constipation, vomiting, diarrhoea, pyrexia, dry mouth, flushing, and nasal congestion. At the week 24/exit visit, 52.3% (95% confidence interval [CI] 43.7–60.9) of patients had an at least three-point decrease in mTDS from baseline and were classified as responders to treatment with oral glycopyrrolate solution, thus demonstrated glycopyrrolate efficacy in the drooling treatment [44].

The same conclusion was obtained by the randomized phase III evaluation of glycopyrrolate safety and efficacy, performed by Robert S. Zeller et al. [45] and published as "Randomized Phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions", in 2012. This study had the same outcomes and endpoints and compared glycopyrrolate to a placebo. Thirty-eight patients aged 3–23 years weighing at least 27 lb (12.2 kg) with severe drooling (clothing damp 5–7 days/week) were randomized to glycopyrrolate (n.=20), 0.02–0.1 mg/kg three times a day, or matching placebo (n.=18) [45].

Responder rate was significantly higher for the glycopyrrolate (14/19; 73.7%) than for the placebo (3/17; 17.6%) group ($p = 0.0011$), with improvements starting 2 weeks after treatment initiation [45]. Mean improvements in mTDS at week 8 were significantly greater in the glycopyrrolate than in the placebo group (3.94 ± 1.95 vs 0.71 ± 2.14 points; $p = 0.0001$). In addition, 84% of physicians and 100% of parents/caregivers regarded glycopyrrolate as worthwhile compared with 41% and 56%, respectively, for placebo ($p = 0.014$). Most frequently reported treatment-emergent adverse events (glycopyrrolate vs placebo) were dry mouth, constipation, and vomiting [45].

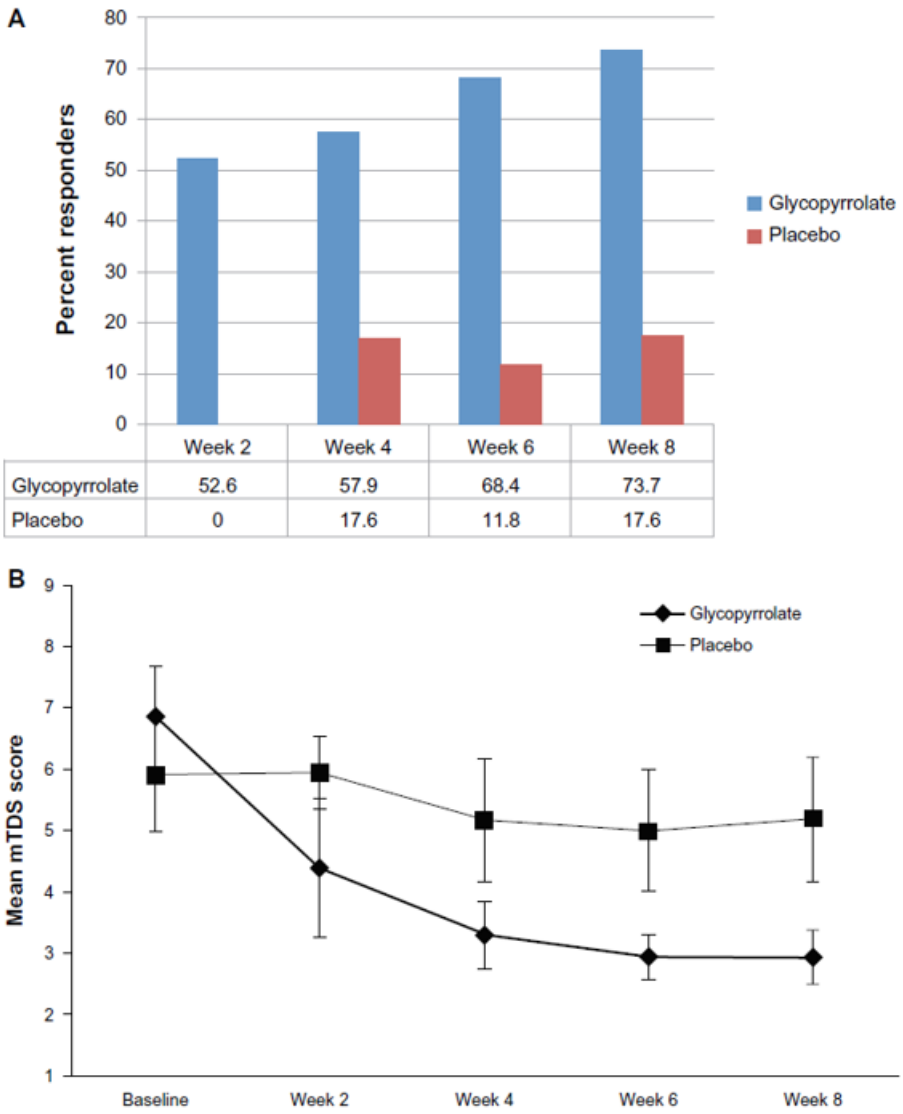


Fig. 2.5 (A) description of percent responders; (B) mean mTDS scores over time. From: Robert S. Zeller et al, "Randomized Phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions" [45].

Susan M. Reid et al. [33], in "Anticholinergic medications for reducing drooling in children with developmental disability" evaluated the effectiveness of three anticholinergic medications in reducing drooling in children with developmental disabilities (such as cerebral palsy, intellectual disability, and autism spectrum disorder), the frequency and nature of side effects, and their impact on treatment discontinuation. The study was conducted at The Royal Children's Hospital and Murdoch Children's Research Institute in Victoria, Australia [33]. They recruited 110 children (71 males, 39 females; mean age 8y 5mo [S.D. 4y 3mo],

range 1y 11mo–18y 11mo) with drooling and neurological impairment and prescribed them medications for 52 weeks or until the drug discontinuation. The medications prescribed were benzhexol hydrochloride, glycopyrrolate, and scopolamine patches [33]. Unless previously tried, benzhexol hydrochloride was the first-line treatment. Carers provided information on compliance, drooling (using a 5-point scale [much improved, improved, no change, worse, much worse] and the DIS), and adverse drug effects [33].

Eighty-one children were prescribed benzhexol, but six never took the drug. One week after commencing benzhexol, 59 (79%) carers rated the perceived change in drooling as improved, 14 as no change, and two as worse. Drooling was rated as improved for 79% of participants using the carer rating and for 60% using a minimum clinically important difference of 12.5 points on the DIS [33]. Sixty-six (88%) carers reported at least one adverse side effect presumed due to benzhexol, such as irritability, gastrointestinal problems, skin changes, visual problems, and increased difficulties with swallowing, but behavioral changes and seizures were considered to have a major impact in most cases [33].

Glycopyrrolate was prescribed to a group of 62 children. After 1 week on glycopyrrolate, 44 (73%) carers rated the child's drooling as improved, 11 as unchanged, and five as worse [33]. On the DIS, 35 (58%) were rated as improved [33]. The carers of 48 (77%) children reported at least one adverse side effect. Gastrointestinal (especially constipation) and behavioral changes were the most frequently reported (45% and 42% respectively).

Scopolamine patches were prescribed to 17 participants. There was a significant decrease in mean total DIS scores from 63.8 (S.D. 14.4) at baseline to 43.2 (S.D. 17.8) at week 1 (p = 0.023) [33]. Carers of 13 children reported at least one adverse side effect. Constipation, skin reactions, and behavioral changes (in four, eight, and nine participants respectively), were the most frequently reported side effects [33].

Based on DIS scores, carer rating, and reasons for ceasing medication, glycopyrrolate had the lowest failure rate of the three medications (Fig. 2.6). Glycopyrrolate was also associated with fewer adverse side effects apart from urinary issues (Fig. 2.7) [33].

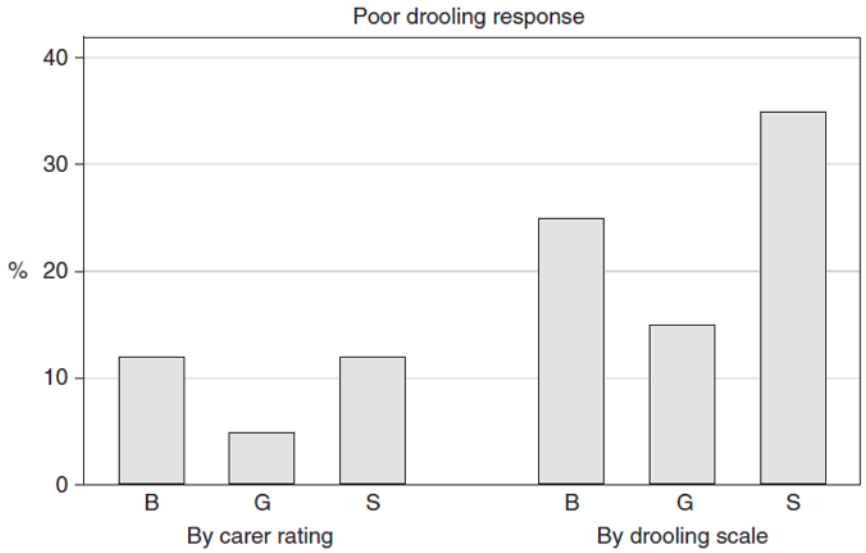


Fig. 2.6 Drugs effectiveness in reducing drooling: the medication that presented the minor percentage of poor drooling response is represented by glycopyrrolate [33]. B, benzexhol; G, glycopyrrolate; S, scopolamine. From: Susan M. Reid et al., "Anticholinergic medications for reducing drooling in children with developmental disability" [33].

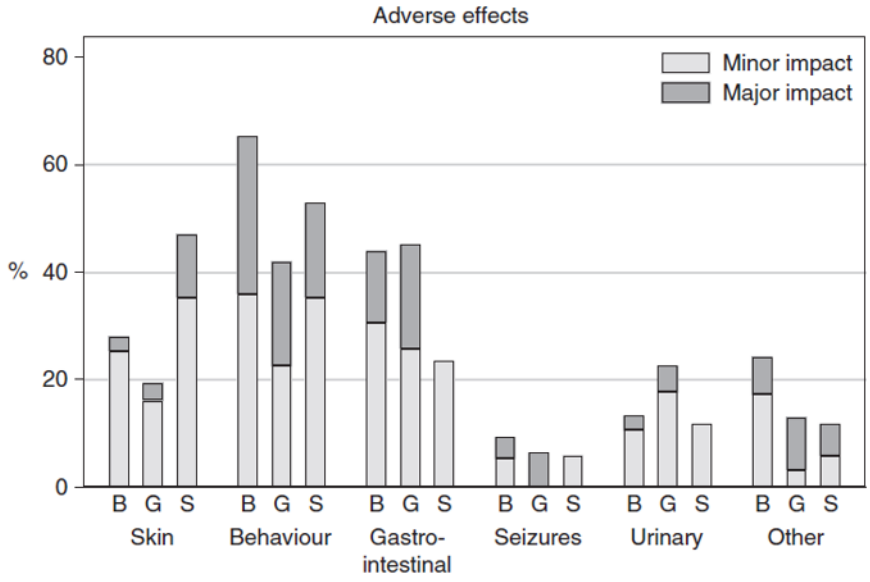


Fig. 2.7 Comparison of medications for frequency of adverse side effects [33]. B, benzhexol; G, glycopyrrolate; S, scopolamine. From: Susan M. Reid et al., "Anticholinergic medications for reducing drooling in children with developmental disability" [33].

Chapter 3

A real-life experience in patients

3.1 Motivations

The introduction of novel treatments for drooling in children represents a crucial step to contrast this condition. This aspect is motivated by the observation that current methods are not experimentally grounded and lack of reliable metrics capable of assessing their efficacy. Therefore, a key enabler for new efficient therapies stands in the introduction of accurate and robust scales to measure their effects on drooling. Nowadays, there does not exist any universally accepted method to rigorously measure sialorrhea. Furthermore, existing objective approaches do not take into account a key parameter: the overall patient's quality of life. This is a particularly important aspect since, as we discussed in the previous sections, sialorrhea has a significant impact on the patient's every-day life. This motivates the application of subjective scales to the evaluation of treatments effectiveness.
A relatively small number of clinical trials has been carried out over the last two decades and many of them base their evaluation of subjective scales, as described in 2.5. The goal of this study is to provide an experimental analysis aimed at quantifying the level of informativeness of the aforementioned subjective methods.

3.2 Methods

Setting

The study was conducted in the neurology department of the pediatric hospital "Istituto Giannina Gaslini", in Genoa. It lasted from February 2020 to June 2020. In order to amplify the number of participants and to obtain more significant results, the study included data

collected from September 2019 to November 2019 in the neurology department of the pediatric hospital "Azienda Ospedaliera Universitaria Federico II", in Napoli.

Instruments

The study was conducted using three subjective scales: the Drooling Severity and Frequency Scale (DSFS, Tab. 1.15), the modified Teachers' Drooling Scale (mTDS, Tab. 1.16), and the Drooling Impact Scale (DIS, Fig. 1.8). These three scales represent the subjective instruments for measuring sialorrhea currently present in the literature and used both from a clinical and experimental point of view. However, they exist only in English, we have therefore translated them, to be able to perform them on Italian-speaking patients.

The Drooling Severity and Frequency Scale (DSFS, Tab. 1.15) is a rapid and simple method to assess drooling frequency and severity. The clinician during the physical examination, or the patient's parents or caregivers are invited to select one of the options reported on the scale, regarding the severity and frequency of drooling. The total score ranges from 2 to 9 and is obtained by the sum of two separated scores (Drooling Frequency Scale, from 1 to 4 points; and Drooling Severity Scale, from 1 to 5 points).

The modified Teachers' Drooling Scale (mTDS, Tab. 1.16) is composed of the same items of the DSFS but reunited in a single sentence, which describes both the severity and the frequency of drooling. The advantage of this scale is represented by its simplicity, which makes this method more appropriate to direct parents' administration. While DSFS is especially used by the clinicians, after history and physical examination of the patient, mTDS is usually proposed to the parents or the caregivers, who select the value of the score that best figures the clinical situation of the children (range 1 = Dry: never drools; 9 = Profuse: clothes, hands, trays, and objects become wet, frequently).

The Drooling Impact Scale (DIS, Fig. 1.8) adds essential information regarding children's quality of life. This questionnaire is composed of a list of ten questions, ranging from the severity and frequency of drooling to the impact on the child's life. The parents/caregivers are asked to evaluate how much drooling affects the child's life, social integration and routine. In order to quantify the scale, to each question the parents give a score from one to ten, using a *Number Rating Scale* (NRS) or a *Visual Analogue Scale* (VAS). The total score ranges from 10 to 100 points. Since the great variability of the items, we divided the Drooling Impact Scale (DIS) into five domains, as follows:

Domain 1 (d1) - Severity, items 1 and 2

Domain 2 (d2) - Level of care, items 3, 6 and 8

Domain 3 (d3) - Complications, items 4 and 5

Domain 4 (d4) - Impact on the child's life, items 7 and 9

Domain 5 (d5)- Impact on family life, item 10.

Recruitment of participants and data collection

We collected children (age range 1-17y) affected by a neurological disorder with a past/present clinical history of drooling. During the hospitalization or the Day Hospital, the patients were subjected to the questionnaires. In particular, in Genoa, all three questionnaires were administered, whereas in Napoli only DIS and DSFS. The Drooling Impact Scale (DIS) and the modified Teachers' Drooling Scale (mTDS) were compiled directly by the parents or caregivers, whereas the Drooling Severity and Frequency Scale (DSFS) is completed by the clinicians, after the patient's examination. We did not administer the scale directly to the children because of their disability in communication or cognition.

Data analysis

For each participant of the study, we collected a list of data: age, sex, diagnosis, comorbidities, pharmacological therapy, DSFS score, DIS score, and mTDS score. As regards comorbidities, we focused on the presence or absence of epilepsy. Therapy refers to the treatment performed by the patient for his neurological disorder, including any anti-drooling treatments. The DIS score was divided into two groups: the *DIS-total score* (DIS-tot), which represents the total DIS score, and the *DIS-domain score* (DIS-d1/d5), which represents the score of a single domain. We analyzed the data as follows (Tab. 3.1):

- average, median and standard deviation (S.D.) for age
- absolute and relative frequency (%) for sex and diagnosis
- average, median, and standard deviation (S.D.) for DSFS score, DIS-tot score, DIS-d1/5 score, and mTDS score.

The analysis of the patients' data	
Data	*Analysis*
Age	average, median, standard deviation (S.D.)
Sex	absolute and relative frequency (%)
Diagnosis	absolute and relative frequency (%)
Epilepsy	absolute and relative frequency (%)
Anti-drooling therapy	absolute and relative frequency (%)
DSFS score DIS-tot score DIS-d1/5 score mTDS score	average, median, standard deviation (S.D.)

Table 3.1 List of collected data and respectively analysis.

We used the *Pearson's correlation* (also known as *Pearson product-moment correlation - PPMC*), to verify the correlation between:

- DSFS score and DIS-tot score
- DSFS score and DIS-d1/5 score
- DSFS score and mTDS score
- age and DSFS score
- age and DIS-tot score
- age and mTDS score.

The Pearson correlation is a parametric measure which produces the coefficient r. The r coefficient describes the linear correlation between two continuous variables. In particular, it indicates whether the linear correlation exists, its strength, and its direction. The value of r ranges from -1 to 1. The sign indicates the direction of the linear correlation:

-1 = perfectly negative linear relationship

0 = no relationship

+1 = perfectly positive linear relationship.

The strength of the linear relationship is indicated as follows:

$0 < r < 0.3$ weak correlation

$0.3 < r < 0.7$ moderate correlation

$r > 0.7$ strong correlation.

Participants were subdivided into two groups: the one that presents a DSFS score 2-5, and the one that presents a DSFS score 6-9. We calculated the absolute and relative frequency of the patients in these two different groups. Therefore, we applied the non-parametric *Mann-Whitney U test* to verify and quantify the difference between the DIS scores obtained in the patients of the two groups. It is established that the significance level corresponds to $p < 0.05$.

Finally, we calculated the absolute number and the percentage of epileptic patients in the two groups mentioned above.

3.3 Results

We enrolled 31 children (age range 1-17y; age average 7y 3mo; S.D. 4y 5mo) who present drooling associated with neurological disorders. In particular:

10 with an acquired neurological disorder (3 CP and spastic tetraparesis, 2 herpetic encephalitis, 2 psychomotor development retardation, 1 CP and periventricular leukomalacia, 1 CP and neurofibromatosis type 1, 1 autoimmune encephalitis)

19 with a genetic-malformative disorder (8 epileptic encephalopathy, 2 genetic syndrome associated with microdeletion, 2 Angelman syndrome, 1 Mowat-Wilson syndrome, 1 Pallister-Kilian syndrome, 1 cromosomopathy, 1 L1CAM syndrome, 1 agenesis of the corpus callosum, 1 Potocki-Lupski syndrome, 1 DDX3X syndrome)

2 with a muscular disease (1 congenital muscular dystrophy, 1 congenital myopathy).

The characteristics of the participants are reported in Tab. 3.2.

Patients' characteristics			
Age	*average 7y 3mo; median 6y; S.D. 4y 5mo*	**Number**	**%**
Sex	*Female*	10	32%
	Male	21	68%
Diagnosis	*Neurological acquired causes*	10	32%
	Neurological congenital causes	19	61%
	Muscular causes	2	7%
Epilepsy	*Epileptic*	20	65%
	Non-epileptic	11	35%
Therapy	*With anti-drooling agents*	3	10%
	Without anti-drooling agents	28	90%

Table 3.2 Analysis of age, sex, diagnosis, epilepsy and therapy in the study group. y, years; mo, months; S.D., standard deviation.

Of these 31 patients, 15 underwent DSFS and DIS scales only, while 16 underwent DSFS, DIS, and mTDS scales. Consequently, the group of patients undergoing mTDS scale is statistically less extensive.

After collecting the scores obtained by each patient on the subjective scales, we analyzed them, as shown in the Tab. 3.3. Tab. 3.3 reports the mean, median, and standard deviation (S.D.) values for each score. The next step was to cross these parameters, to study their correlation through the Pearson index (r).

Patient	**Age (y,mo)**	**DSFS (min 2, max 9)**	**DIS-tot (min 10, max 100)**	**mTDS (min 1, max 9)**
1	6	9	73	
2	16	9	69	
3	10	8	48	
4	14	8	57	
5	17	7	35	
6	12	7	60	
7	5	6	39	
8	13	6	18	
9	12	5	44	
10	4	5	49	
11	9	5	24	
12	10	4	10	
13	8	2	10	
14	6	2	10	
15	2	2	10	
16	1	7	48	5
17	3	6	46	2
18	3	4	33	4
19	5	9	85	9
20	3	4	20	2
21	10	2	10	1
22	7	2	10	1
23	8	10	61	8
24	6	8	100	9
25	2	6	31	5
26	4	8	67	9
27	3	7	50	8
28	2	8	58	9
29	12	6	45	5
30	8	6	52	6
31	4	8	70	9
Avarage	7,3	6	43.3	5.75
Median	6	6	46	5.5
S.D.	4,5	2.35	24.2	3.1
Pearson		r = 0.12		
			r = 0.05	
				r = -0.20
			r = 0.86	
				r = 0.88
				r = 0.87

Table 3.3 Patients' DSFS, DIS-tot and mTDS scores and their correlations. DSFS, drooling severity and frequency scale; DIS-tot, drooling impact scale-total; mTDS, modified teachers' drooling scale; y, years; mo, months; min, minimum; max, maximum; r, Pearson correlation coefficient; S.D., standard deviation.

We obtained a strong correlation between DSFS and DIS-tot ($r = 0.86$), between DSFS and mTDS ($r = 0.88$), and between DIS-tot and mTDS ($r = 0.87$). The correlation between

age and DSFS is weak (r = 0.12) and no linear relationship was found between age and DIS-tot. Age and mTDS score show a negative linear relationship (r = -0.20).

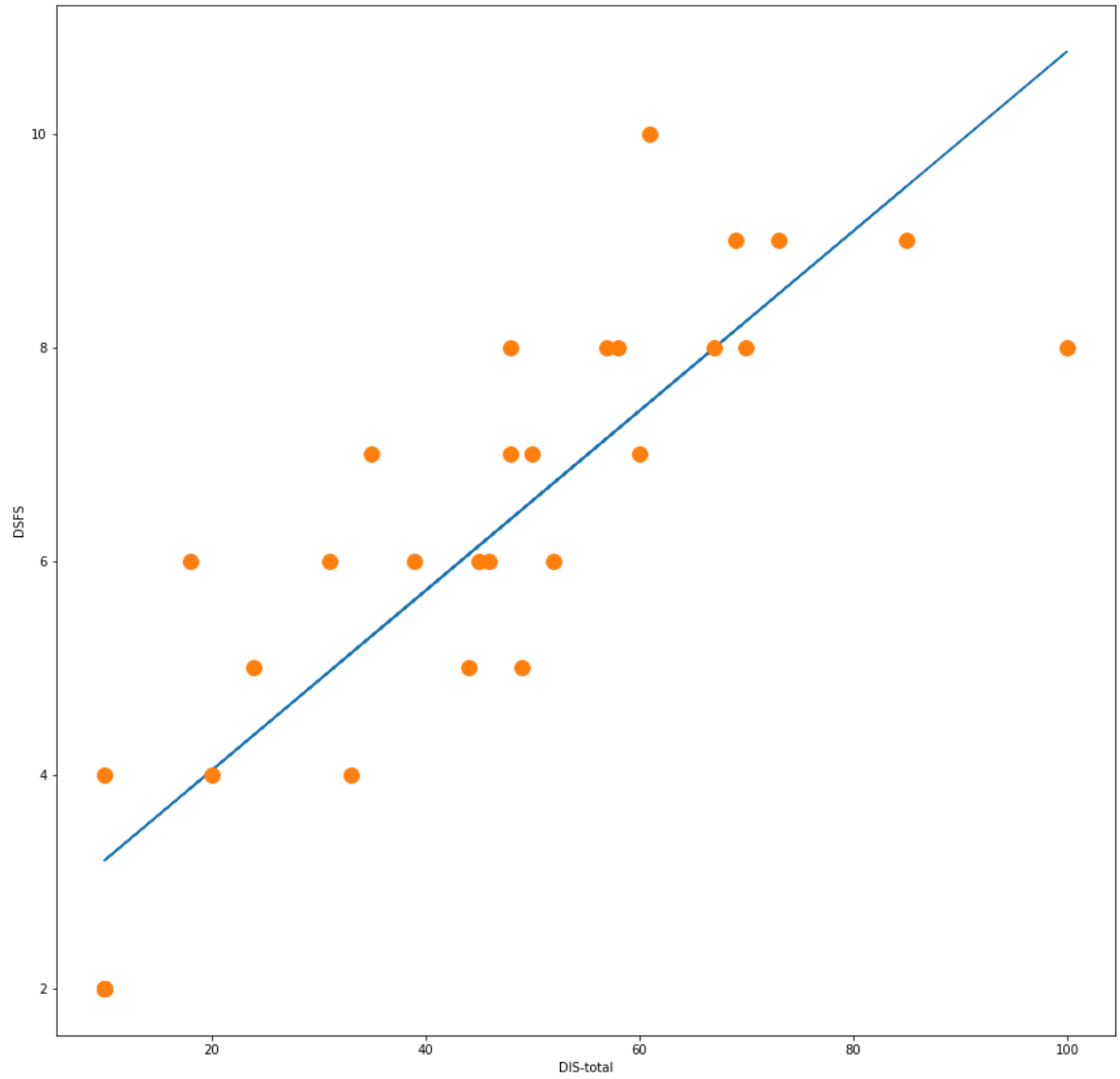


Fig. 3.1 The linear positive relationship between DSFS score and DIS-tot score in the participants of the study. This graphic representation confirms the above: the correlation between the two variables is strongly positive ($r > 0.3$).

Considering the variability of the scores on the different items of the DIS questionnaire, we calculated the correlations between each DIS-d and the other scales (DSFS and mTDS).

Patient	DSFS (min 2, max 9)	DIS-d1 Severity (min 2, max 20)	DIS-d2 Level of care (min 3, max 30)	DIS-d3 Complications (min 2, max 20)	DIS-d4 Impact on the child's life (min 2, max 20)	DIS-d5 Impact on family life (min 1, max 10)
1	9	20	24	8	11	10
2	9	18	30	13	2	6
3	8	16	20	3	2	7
4	8	18	18	9	2	10
5	7	16	14	2	2	1
6	7	13	21	11	8	7
7	6	13	8	11	2	5
8	6	6	3	2	4	3
9	5	15	16	6	2	5
10	5	15	13	10	2	9
11	5	12	7	2	2	1
12	4	2	3	2	2	1
13	2	2	3	2	2	1
14	2	2	3	2	2	1
15	2	2	3	2	2	1
16	7	10	21	2	8	7
17	6	10	18	6	7	5
18	4	9	8	5	6	5
19	9	20	30	8	17	10
20	4	2	11	2	3	2
21	2	2	3	2	2	1
22	2	2	3	2	2	1
23	10	15	15	6	15	10
24	8	20	30	20	20	10
25	6	13	12	2	2	2
26	8	18	25	5	10	9
27	7	15	18	10	5	2
28	8	18	23	6	2	9
29	6	10	11	6	12	6
30	6	18	12	6	15	1
31	8	20	30	8	2	10
Average	6	12	14.70	5.83	5.64	5.09
Median	6	13	14	6	2	5
S.D.	2.35	6.49	9.11	4.28	5.31	3.59
Pearson		r = 0.87				
			r = 0.84			
				r = 0.53		
					r = 0.48	
						r = 0.77

Table 3.4 Patients' DSFS, DIS-d1/5 scores and their correlations. DSFS, drooling severity and frequency scale; DIS-d1/5, drooling impact scale domains 1/5; min, minimum; max, maximum; S.D., standard deviation; r, Pearson correlation coefficient.

Tab. 3.4 shows the results obtained in calculating the correlation between DIS-d1/5 and DSFS. We obtained a strong correlation between DSFS and *Severity* ($r = 0.87$), *Level of care* ($r = 0.84$), and *Impact on family life* ($r = 0.77$). Instead there is a moderate correlation between DSFS and *Complications* ($r = 0.53$) and *Impact on the child's life* ($r = 0.48$).

Patient	mTDS (min 1, max 9)	DIS-d1 Severity (min 2, max 20)	DIS-d2 Level of care (min 3, max 30)	DIS-d3 Complications (min 2, max 20)	DIS-d4 Impact on the child's life (min 2, max 20)	DIS-d5 Impact on family life (min 1, max 10)
16	5	10	21	2	8	7
17	2	10	18	6	7	5
18	4	9	8	5	6	5
19	9	20	30	8	17	10
20	2	2	11	2	3	2
21	1	2	3	2	2	1
22	1	2	3	2	2	1
23	8	15	15	6	15	10
24	9	20	30	20	20	10
25	5	13	12	2	2	2
26	9	18	25	5	10	9
27	8	15	18	10	5	2
28	9	18	23	6	2	9
29	5	10	11	6	12	6
30	6	18	12	6	15	1
31	9	20	30	8	2	10
Average	5.75	12	14.70	5.83	5.64	5.09
Median	5.5	13	14	6	2	5
S.D.	3.1	6.49	9.11	4.28	5.31	3.59
Pearson		r = 0.93				
			r = 0.82			
				r = 0.60		
					r = 0.46	
						r = 0.75

Table 3.5 Patients' mTDS and DIS-d1/5 scores and their correlations. mTDS, modified teachers' drooling scale; DIS-d1/5, drooling impact scale domains 1/5; min, minimum; max, maximum; S.D., standard deviation; r, Pearson correlation coefficient.

Tab. 3.5 shows the results obtained in calculating the correlation between DIS-d1/5 and mTDS. We obtained a strong correlation between mTDS and *Severity* ($r = 0.93$) and *Level of care* ($r = 0.82$). However, the correlation is moderate between mTDS and *Complications* ($r = 0.60$) and *Impact on the child's life* ($r = 0.46$).

In addition, we divided the patients into two groups, based on the DSFS score:

- *group A* includes the DIS scores of subjects with a DSFS score between 2 and 5 (mild drooling)
- *group B* includes the DIS scores of subjects with a DSFS score between 6 and 9 (moderate-to-severe drooling).

Participants of groups A and B are listed in Tab. 3.6 (number and %).

Patients	**Group A DSFS 2-5**	**Group B DSFS 6-9**
Number	11	20
%	35	65

Table 3.6 Patients' subdivision into two groups (A and B) according to the drooling severity calculated with the DSFS scale. DSFS, drooling severity and frequency scale.

The Mann-Whitney test allowed to highlight significant differences between the two groups for the total impact (assessed by the DIS-tot score), and for each of the domains (assessed by the DIS-d1/5 scores), where $p < 0.05$. In Tab. 3.7, the obtained values were entered.

Parameter	**Group A vs. Group B**
DIS-tot	U = 16 $p = 5 \times 10^{-5}$
DIS-d1 *Severity*	U = 21 $p = 1 \times 10^{-4}$
DIS-d2 *Level of care*	U = 20 $p = 1 \times 10^{-4}$
DIS-d3 *Complications*	U = 45 $p = 0.03$
DIS-d4 *Impact on the child's life*	U = 54 p = 0.006
DIS-d5 *Impact on family life*	U = 35 $p = 8 \times 10^{-4}$

Table 3.7 Values that express the difference in DIS scores (total and domains) between patients with mild drooling and those with moderate-to-severe drooling. DIS-tot, drooling impact scale-total; DIS-d1/5, drooling impact scale domain 1/5; U, Mann-Whitney test; p, p value.

For each of the parameters listed in the Tab. 3.7 $p < 0.05$. It can, therefore, be deduced that the two groups have a significant difference in each of the above parameters.

Finally, to verify if there is an association between epilepsy and drooling, a comparison was made between epileptic and non-epileptic patients. As reported in the Tab. 3.8, it cannot be deduced that there is a particular association between the two clinical conditions.

Group	Epileptic patients		Non-epileptic patients	
	Number	*%*	*Number*	*%*
A	7	64	4	36
B	13	65	7	35

Table 3.8 Number and percentage of patients with or without sialorrhea in relation to the presence or absence of epilepsy.

3.4 Discussion

The study was aimed at analyzing current methods of subjective evaluation of sialorrhea to improve them and therefore promote better patient management in the future. An ideal subjective method should not be limited to assessing the direct characteristics of drooling, such as its frequency and severity, but should also include an adequate assessment of the patient as a whole. And this is how topics such as the number of bibs or clothes changed per day, the level of interpersonal contacts, and the stress load of the caregiver become essential parameters in the management of a patient who drools.

The subjective scales we used proved to be quick and simple, requiring a maximum of 10 minutes to complete the questionnaire. Thanks to their simplicity, the DIS and mTDS scales were in some cases compiled directly by the patients' parents, who did not show any perplexity in understanding the items. The only necessary step was the translation into Italian of the questionnaires, currently available only in English. The only difficulty sometimes encountered by parents was the understanding of the NRS, which is why the use of the VAS (Visual Analogue Scale) is suggested.

The strong correlation existing between the DSFS, DIS, and mTDS scales confirms their diagnostic and prognostic validity. Their effectiveness has proven to be significantly interchangeable for almost all aspects assessed in the questionnaires. However, not all scales fully analyze the patient's clinical condition. Indeed, by comparing the DSFS scale with the domains of the DIS scale, there was a strong correlation between DSFS and the severity of drooling, the burden of care, and the impact on the family. However, the correlation remains moderate between DSFS and complications and impact on the family. This slight discrepancy primarily highlights the shortcomings of DSFS in assessing the clinical impact of drooling, both physically and psychologically. The strong correlation with the impact on the family, to the detriment of the moderate correlation with the impact on the patient himself, could

be explained by the fact that the questionnaire is obviously completed by the parent and not directly by the patient. These considerations are supported by the comparison between mTDS and the subdomains of DIS. We obtained the same results: the correlation is moderate both with complications and with the impact on the child.

As regards the differences in patients with mild drooling and those with moderate or severe drooling, the two groups proved to be completely distinct in every respect. The adequate evaluation of the parents in terms of severity and frequency of sialorrhea has demonstrated their accurate awareness of the pathology. Patients with more severe drooling, and therefore with DSFS 6-9, scored higher in each domain of the DIS. While, subjects with mild drooling, or with DSFS 2-5, receive a lower level of care, have fewer complications, and also a lesser impact on the life of both the child and the family.

The life of patients with severe drooling is therefore clearly influenced by the physical and psychological complications of sialorrhea. Our study did not reveal any particular conditions associated with this specific group of patients. Epilepsy has the same frequency both in subjects with severe sialorrhea and in those with mild sialorrhea. Even age does not seem to have a specific correlation with subjective scales, as shown by the low r values ($r < 0.3$) reported in the previous section. Patients with severe drooling, therefore, remain neurological patients with a serious clinical and social disability, well recognized by parents and well suffered by the child and the family in general. In conclusion, the subjective scales proved adequate for the evaluation of sialorrhea and its clinical impact.

The image below (Fig. 3.2) is a graphical representation of the correlations that we have analyzed in the previous section with the Pearson index (r). There is no correlation between the patient's age and the scores obtained on the subjective measurement scales of sialorrhea. Looking at the image, the more or less strong correlation between the scores of the three scales is clear. This fact is a confirmation of the validity and accuracy of the scales in the evaluation of sialorrhea.

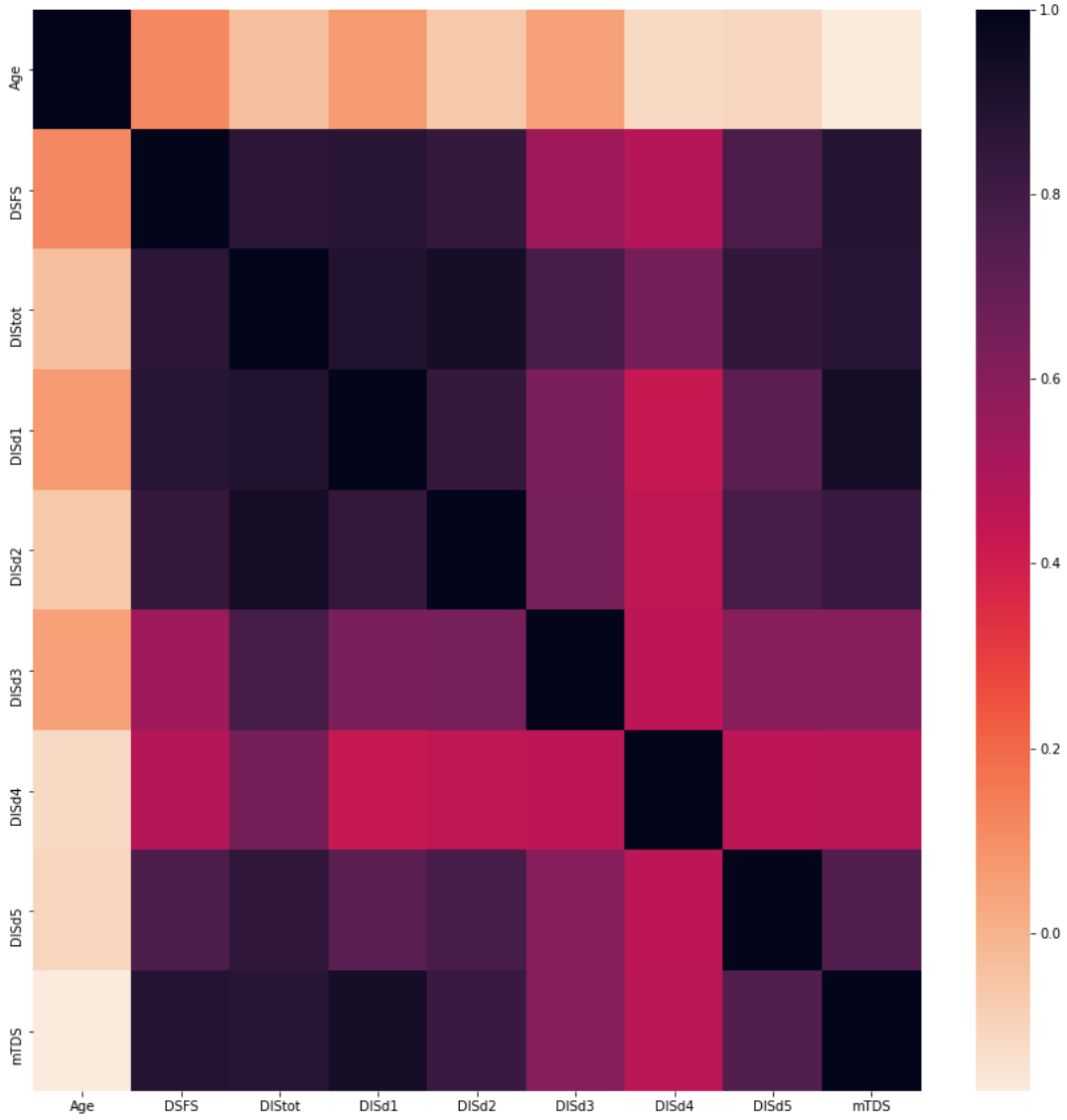


Fig. 3.2 This heat-map shows the correlations existing between the parameters of the patients. The higher the Pearson index ($r > 0.7$), the stronger the correlation between the two variables on the x and y-axis, and the greater the intensity of the color on the map.

The currently most complete subjective scale has proved to be the DIS scale, thanks to its greater variability and its different subdomains. Indeed, it is not possible to correctly evaluate drooling without analyzing its impact on the quality of life and complications. However, the DIS scale also has some flaws:

1. There is no validated and standardized questionnaire in a language other than English. The translation into Italian of the questionnaire can create bias and make questionnaires made in different languages less comparable.

2. The questions in the questionnaire refer only to the type of anterior drooling, while there are no questions that allow investigating also the posterior drooling, which in terms of complications could be more complex than the anterior one and significantly impact the life of the patient and caregivers.

3. The questions relating to the psycho-social impact are rather generic, therefore the items aimed at examining the actual consequences in the context of social interactions and the psycho-affective experience of the patient and caregivers are missing. This is because the DIS scale was designated by the authors to quantify the benefits of a short-medium term intervention for sialorrhea and that the items included in the scale were chosen based on the property of changing in quickly after an operation. Changes in social interaction and self-esteem, however, occur more gradually and may not occur in the short to medium term.

4. The questionnaire does not include any questions regarding the patient's anti-drooling treatment and this makes the DIS scale less accurate in assessing the effectiveness and safety of an anti-sialorrhea treatment.

5. The questions always refer to the parents, not including any caregivers or the patient himself in the evaluation.

6. Each question requires a score from 1 to 10, through NRS or VAS. This makes it less understandable and interpretable in some cases by parents and especially children.

Chapter 4

Perspectives

The purpose of the study was to analyze the subjective scales for the measurement of sialorrhea and verify its accuracy in the diagnosis of sialorrhea, in the assessment of the impact on the life of the patient and the family, and the evaluation of the efficacy and safety of a treatment. From the considerations made previously, a good accuracy of all three scales emerged in the diagnosis of sialorrhea. The only scale capable of accurately assessing the physical and socio-psychological impact of drooling is the DIS scale. In the previous chapter, however, we reported the defects of the aforementioned scale and its inadequacy in the evaluation of some fundamental aspects, including the efficacy and safety of a treatment. This chapter intends to suggest any changes and additions to the DIS scale, in order to improve it and make it more suitable for the management of the patient with sialorrhea as a whole.

Language

The first suggestion consists of the validation and standardization of a questionnaire written in Italian, in order to standardize its administration in Italian and non-Italian patients. Fig. 4.1 shows an example of DIS scale translated into the Italian language.

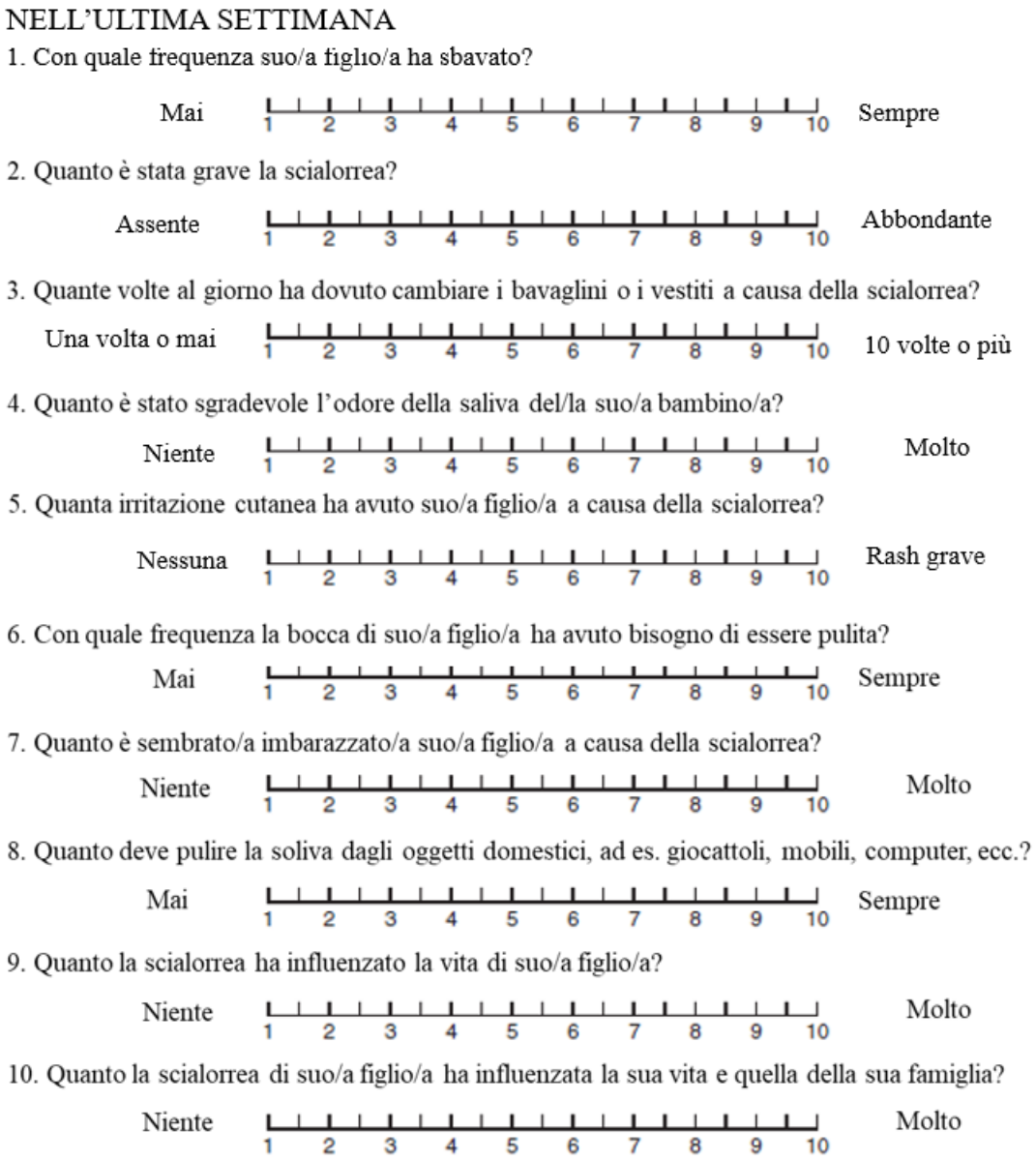


Fig. 4.1 The DIS scale translated into Italian which we used for our study.

Domains 1, 2 - Severity, Level of care

The DIS scale is an accurate assessment of these clinical aspects. Consequently, no changes are suggested in these two domains.

Domain 3 - Complications

This domain of the DIS scale examines the most common physical complications in the patient with anterior drooling, i.e. unpleasant odor and skin irritation. These consequences

derive from the drainage of saliva from the lips to the chin and beyond. Anterior drooling is the most frequent form of drooling, especially in neurological patients. However, posterior drooling, represented by the discharge of saliva from the oral cavity to the airways, in turn, requires an evaluation. Complications of posterior drooling can be much more serious and include dyspnea, cough, and aspiration pneumonia. For these reasons, it is suggested to insert two questions on the DIS scale which also examine these two complications (cough and respiratory problems), as shown in Fig. 4.2.

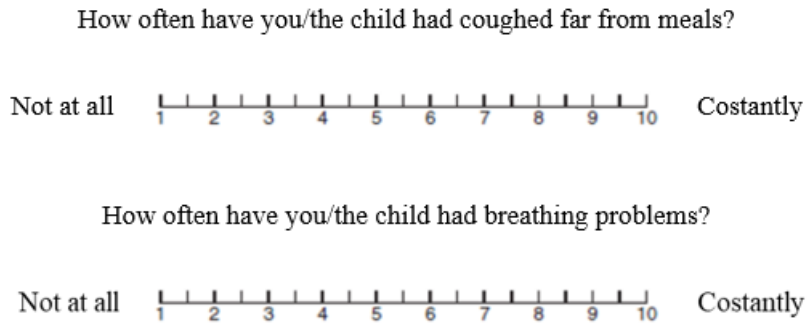


Fig. 4.2 The two additional questions that analyze the complications of posterior drooling.

Domains 4, 5 - Impact on child's life, Impact on family life

As reported in the previous chapter, the DIS scale is the only one of the three scales to analyze these important consequences of drooling. The sociopsychological sphere of the patient and the family is particularly affected by drooling, in a very wide and varied way. For this reason, the questions of the DIS questionnaire are too general and a more specific version is suggested, dedicated both to the child and to the parents, in order to analyze in greater detail one of the hottest aspects of the sialorrhea problem (Fig. 4.3).

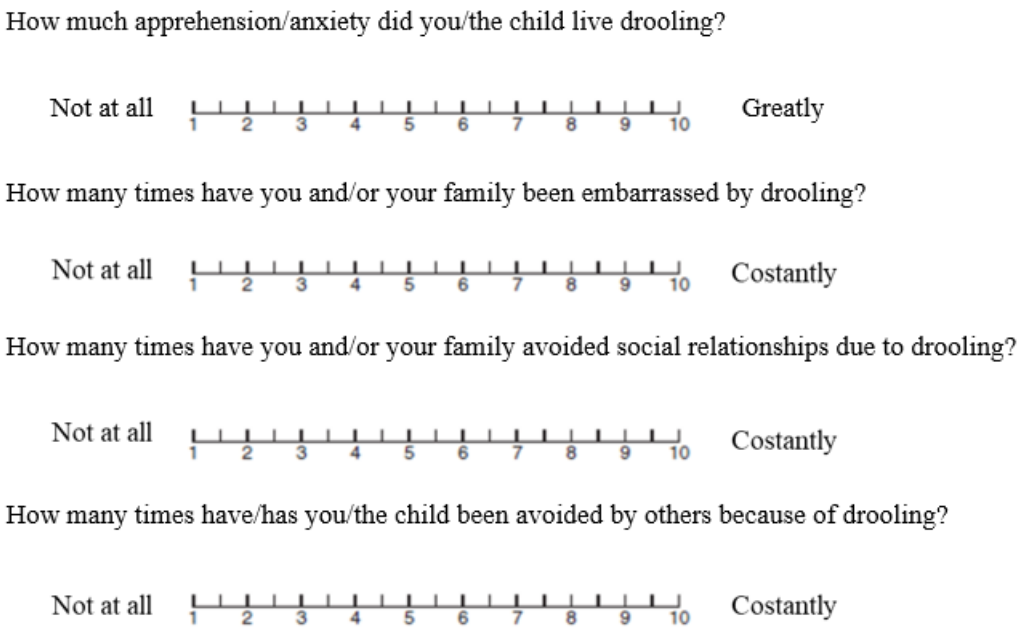


Fig. 4.3 Additional questions that analyze in more detail the emotional, social and psychological impact of drooling on the patient and his family.

Treatment efficacy and safety

The DIS scale was used as an evaluation parameter in clinical trials on the efficacy and safety of anti-drooling treatments. This requires that this questionnaire is able to accurately evaluate the effects of treatment. The scale adequately assesses drooling in general terms but does not have any specific questions regarding treatment. A question directed to the patient or parent about the effects of the treatment can, therefore, be considered as a suggestion for increasing the accuracy of the scale. Fig. 4.4 shows an example of a question to add to the questionnaire. Another suggestion, albeit longer and more complex, may be to fill in two questionnaires, one before treatment and one after treatment.

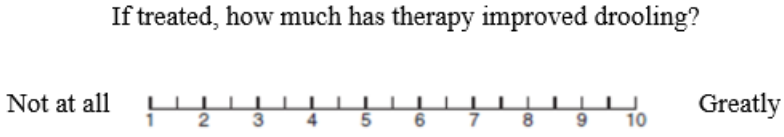


Fig. 4.4 The additional question that may increase the accuracy of the DIS scale in evaluating the effectiveness of anti-drooling therapy.

Administration and interpretation of the scale

Our study allowed us to highlight some defects of the DIS scale also in its method of administration and interpretation. The first difficulty encountered in simply reading the questionnaire to the patient concerns the formulation of the questions. Indeed, each question is always referred to the parent, without therefore considering the patient's ability to answer the questions and not even the possibility that the parent is not the caregiver. Our suggestion is therefore to produce a version of the DIS scale in which each question is addressed not only to the parent but also to the caregiver or the child himself. As for the interpretation of the questionnaire, the VAS and NRS are adequate for most parents. However, the patient's evaluation of the problem can constitute an important improvement in the scale, especially as regards aspects of personal life. Therefore, to promote the administration of the questionnaire directly to children, an even more simplified version of the scale can be proposed, which is not based on the NRS, nor on the VAS, but on a *"Faces" Drooling Rating Scale*, taking for example the same existing scale for pain assessment in pediatric or intellectually disabled patients.

DROOLING IMPACT SCALE (DIS)

OVER THE LAST WEEK

SEVERITY & FREQUENCY

1. How frequently did you/the child dribble?
2. How severe was the drooling?

LEVEL of CARE

3. How many times of day did you have to change bibs or clothing due to drooling?
4. How frequently did your/the child's mouth need wiping?
5. How much did you have to wipe or clean saliva from household items?

COMPLICATIONS

6. How offensive was the smell of your/the child's saliva?
7. How musch skin irritation you/the child presented due to drooling?
8. How often have/has you/the child had coughed far from meals?
9. How often have/has you/the child had respiratory problems?

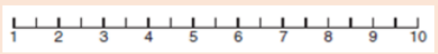
IMPACT ON LIFE

10. How much apprehension/anxiety did you/the child live drooling?
11. How many times have you and/or your family been embaressed by drooling?
12. How many times have you and/or your family avoided social relationships due to drooling?
13. How many times have/has you/the child been avoided by others because of drooling?

TREATMENT

14. If treated, how much has the therapy improved drooling?

Reply with:



1-2 **3-4** **5-6** **7-8** **9-10**

Fig. 4.5 The DIS scale modified according to our suggestions. In the questions section (to the left): the scale has been divided into domains, based on the topic of the questions; the questions are addressed to the parents/caregivers or the patient himself; questions about complications of posterior drooling (8,9), impact on the quality of life (10, 11, 12, 13) and treatment (14) have been added. In the answers section (to the right): in addition to NRS and VAS, a *"Face" Drooling Rating Scale* has been added.

Chapter 5

Conclusions

In our study, we collected pediatric patients suffering from various neurological disorders that manifested a problem that is still little studied and little known today: sialorrhea. The neurological patients affected by drooling belonged to very heterogeneous groups: some were affected by particularly disabling congenital pathologies, others only by epilepsy, and others by pathologies of a variable entity, such as cerebral palsy. Regardless of their underlying condition, the life of each patient was found to be highly influenced by sialorrhea and this was demonstrated by the scores on the subjective scales.

The evaluation of drooling is a fundamental aspect in the management of these children and the purpose of the study was to verify the adequacy of the subjective methods of measuring sialorrhea. Therefore, we compared the subjective scales nowadays present in the literature, namely the DIS, DSFS, and mTDS scales. Each of these scales was effective in the diagnosis of drooling, both in terms of the severity and frequency of the disorder. In addition to diagnosing the problem, a good clinician must also evaluate its complications. The only of the above scales that takes into account the physical complications of drooling is the DIS scale. A strong correlation between these complications and the severity of sialorrhea emerged from our analyzes. The DIS scale, however, only examines the complications of anterior drooling, although the complications of posterior drooling are even more serious. It is therefore up to the clinician to add the evaluation of cough and/or dyspnoea in a drooling patient.

Children suffering from severe drooling, as emerged from our analyzes, need continuous care. Their quality of life is particularly affected, with a series of complications also from a socio-psychological point of view. Often these children are avoided by peers or fail to play or perform normal activities of daily life. They are often ashamed of their saliva and its bad

smell. The only one of the subjective scales that measures the drooling impact on the quality of life is the DIS scale. However, even in this field, the questionnaire presents some deficits: it is too general and refers to a too short period (the last week).

Finally, the last part of the study focused on analyzing the usefulness of subjective scales as a parameter for assessing the effectiveness and safety of anti-drooling treatments. All clinical trials in the literature are based on subjective scales. Indeed, a standardized objective method for the measurement of sialorrhea is unfortunately not yet available and validated. The subjective aspect of the scale helps in the evaluation of drooling as a whole, however, it can be said that none of the three questionnaires refers directly to the patient's treatment.

In conclusion, it is hoped that these considerations will help in the future development of a method of evaluating sialorrhea, its clinical effects, and its treatments as accurately as possible, to manage and treat these young patients correctly and in the best way. The first step is undoubtedly to empower clinicians to face the problem. Our study revealed a very high level of awareness on the part of parents, what is hoped is that the same level of awareness will also be achieved in the future by clinicians and researchers. Only by recognizing the importance of the problem will it be possible to develop new and better methods to treat and manage it for the health of current and future patients.

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