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Microstomia: A Rare but Serious Oral Manifestation of Inherited Disorders

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1. Introduction

Microstomia is a term used to describe a small oral aperture (Stedman, 1976). Trauma, ingestion of caustic substances, electrical and thermal burns of perioral tissues and reconstructive lip surgeries can result in undesired cicatricial scar formation and inhibit adequate mouth opening (Smith et al., 1982). Less commonly, microstomia can also occur as a result of systemic and/or inherited disorders.

The orbicularis oris muscle, the primary muscle of the lips, forms the sphincter around the mouth and the philtral columns (Wust, 2006) The muscular layer is separated from the skin by a thin subcutaneous layer and from the mucosa below by a thin submucosal layer that contains the adnexa, sensory end organs, and lymph nodes (Wust, 2006). In acquired cases, perioral facial traumas may result in scarring and contraction caused by the involvement and infiltration of the complex perioral musculature during the healing process depending on the depth of injury (Wust, 2006). However, in genetic disorder related cases, the etiology of the condition is variable and mostly remains uncertain.

Individuals with microstomia may experience several problems related to speech, nutritional needs, dental hygiene, facial expression and social interaction (Mordjikian, 2002). Additionally, airway and ventilation problems and aspiration can induce fatal consequences during general anaesthesia procedures (Jaminet et al., 2009).

Management of microstomia is a complex treatment modality and demands complex functional and aesthetic requirements of soft tissues of circumoral region. Providing well functioning lips should be the main objective of the treatment and relapses should be prevented to obtain stable and long lasting results (Koymen et al., 2009). Treatment of the latter was based on mainly on surgical techniques, non-surgical approaches or combination of both methods.

It is important to highlight the reconstruction of the orbicular sphincter for adequate lip function beside lip symmetry, which is the main objective of microstomia reconstruction.

The aim of this chapter is to review the genetic diseases associated with microstomia and briefly discusses the surgical and non surgical management options of the condition.

2. Inherited disorders associated with microstomia

2.1 Scleroderma

Scleroderma originates from the Greek words *skleros,* meaning "hard", and *derma,* meaning "skin" (Albilia et al., 2007) This pathologic condition is the initial manifestation of a disease

process better described as progressive systemic sclerosis (PSS), which was named by (Goetz, 1945). It is a multi-system disorder of the connective tissue characterized by vascular disease and the deposition of collagen and other matrix constituents in the skin and other target organs, *i.e.*, the gut, lung, heart, kidney, joints and muscles (Seibold, 2005). Systemic sclerosis process involves damage to the vascular epithelium, immune activation, and increased matrix production. The clinical manifestations of Systemic sclerosis include Raynaud's phenomenon, as well as fibrotic complications of the skin, skeletal muscles, gastrointestinal tract, pulmonary, renal, and cardiac systems. The disease occurs more commonly in women (estimated female to male ratio, 4:1), and the age of peak onset is 30 to 50 years (Steen&Metsger, 1990). The minimum estimated values of incidence and prevalence are 20/million per year and 1,500/million, respectively (Ferri et al., 2002; Hawk&English, 2001).

Although systemic sclerosis is an uncommon autoimmune rheumatic condition affecting connective tissues, it presents great challenges to both medical and dental professionals and has a profound impact on oral health (Albilia et al., 2007). The current classification of systemic sclerosis is based on the extent and pattern of skin sclerosis and reflects the extent of the involvement of organ systems; however this is not highly specific (Albilia et al., 2007). Systemic Sclerosis is subdivided into limited and diffuse cutaneous subtypes. (Table 1) Survival of people with systemic sclerosis mainly depends on the subtype of the disease. Limited cutaneous systemic sclerosis has a 10-year survival rate of 71%; diffuse cutaneous SS, 21%.18 Pulmonary hypertension and scleroderma renal crisis are important prognostic predictors (Trad et al., 2006).

Localized scleroderma
Linear scleroderma
Localized morphea
Generalized morphea
Systemic sclerosis
Limited cutaneous systemic sclerosis
Diffuse cutaneous systemic sclerosis
Systemic sclerosis sine scleroderma
Environmentally induced scleroderma
Overlap syndromes

Table 1. Classification system for progressive systemic sclerosis (adopted from Albilia et al., 2007)

Patients with limited cutaneous systemic sclerosis typically have skin sclerosis that is restricted to the hands, and sometimes the face and neck. They also have prominent vascular manifestations and frequently exhibit features of CREST syndrome. (Table 2) (adopted from Albilia et al., 2007)

Characteristic	Description
Calcinosis cutis	Calcific deposits, usually within the dermis in the extremities and bony prominences, also in deeper periarticular tissues around or within the joints
Raynaud's phenomenon	Triphasic colour changes in the following order: pallor, cyanosis and erythema, representing vaso-constriction, reduced blood flow and reperfusion, respectively
Esophageal dysmotility	Earliest change in the distal esophagus (primarily smooth muscle); an uncoordinated disorganized pattern of contractions resulting in low amplitude or no peristalsis
Sclerodactyly	Fibrosis of the skin of the fingers or toes, associated with atrophy and ulcerations of the fingertips
Telangiectasias	Nonpulsatile macular areas of hemorrhage

Table 2. Features of CREST syndrome (adopted from Albilia et al., 2007)

2.1.1 Physical findings

The first symptom with scleroderma is deformity in the fingers and the toes, caused by a circulation disorder, called the Raynaud phenomenon. The early skin effects begin with the oedema of the face and extremities. The physical findings in progressive systemic sclerosis are:

2.1.1.1 Esophageal dysmotility

Esophageal dysmotility is the most prominent visceral manifestation of PSS, predisposing these persons to gastroesophageal reflux disease, which may be diagnosed first by a dental practitioner. The dental practitioner may then refer the patient to a gastroenterologist for a ph-Probe Test (Barron et al., 2003; Albilia et al., 2007). A barium swallow test is then used to identify hypomotility of the esophagus. Chronic gastroesophageal reflux disease is an important risk factor for aspiration pneumonitis, and potentially pneumonia, and increases the risk of Barrett metaplasia, which in turn increases the risk of esophageal cancer (Barron et al., 2003; Albilia et al., 2007).

2.1.1.2 Pulmonary disease

Pulmonary disease, the second-most common systemic manifestation of PSS, is documented in over 70% of these patients (Albilia et al., 2007). Eventually pulmonary vascular disease develops and results in pulmonary arterial hypertension and subsequent right-sided myocardial hypertrophy (cor pulmonale). For reasons that are unclear, the incidence of lung cancer is higher in patients with progressive sysytemic sclerosis (Winkelmann et al., 1988).

2.1.1.3 Renal disease

Severe and life-threatening renal disease develops in 10% to 15% of patients with PSS. This form of renal involvement is called "scleroderma renal crisis" and is characterized by significant arteriole thickening and constriction, and interstitial collagen deposition,resulting in acute renal failure, marked hypertension and mild proteinuria (Albilia et al., 2007). Patients who have scleroderma without acute renal failure also have physiologic evidence of compromised renal function, which can be estimated readily from the measurement of serum creatinine levels (Livi et al., 2002).

2.1.1.4 Musculoskeletal findings

Patients may have generalized arthralgias and morning stiffness that may mimic other systemic autoimmune diseases. Hand and joint function may decline over time because of skin tightening, rather than arthropathy, and may have a negative impact on daily activities, including maintenance of oral hygiene (Albilia et al., 2007).

2.1.1.5 Orofacial findings and microstomia

In progressive systemic sclerosis patients, subcutaneous collagen deposition in facial skin results in a characteristic smooth, taut, mask-like facies. Nasal alae may become atrophied and result in "mouse-like" facies (Albilia et al., 2007). Other important orofacial manifestations include fibrosis of the salivary and lacrimal glands, and symptoms consistent with dry mouth or xerostomia. Patients may develop dry eyes with keratoconjunctivitis sicca or xerophthalmia(Albilia et al., 2007). This is particularly problematic because scarring of the eyelids results in a chronic widening of the palpebral fissures and inadequate closure of the eyelid, which causes further drying of already dry eyes (Albilia et al., 2007). Inadequate salivary flow compromises buffering within the oral cavity and allows the acidity produced by bacterial metabolism and GERD to erode the dentition. Classic dental radiographic findings of PSS show a thickening of the periodontal ligament or periodontal ligament space (Albilia et al., 2007). Accentuation of periodontal disease also occurs, believed to be due not only to poor oral hygiene but also to the vascular changes associated with the disease itself. With disease progression may come a uniform widening of the periodontal ligaments of all teeth (Albilia et al., 2007).This change seen in a minority of patients occurs at the expense of alveolar bone (lamina dura) rather than root surface. In addition, in a minority of patients there is mandibular bone resorption in non-tooth bearing areas. The inferior border, the posterior border of the ramus, the mandibular angle, and the coronoid and condylar processes may exhibit radiographic evidence of resorption. A blunting of the angles of the mandible, resembling a "tail of the whale," may be seen on an orthopantograph This is believed to be related to an associated muscle atrophy, pressure of tightening of skin overlying the bone and vascular changes (Yenisey et al., 2005). Infrequently, pathologic fractures of the mandible may develop from the mandibular resorption.

Further, facial and mucosal fibrosis compromises oral access because of microstomia, which limits mouth opening in 70% of these patients (Neville et al., 2002). As a consequence, oral hygiene and fabrication of removable dentures are difficult because of limited access and the obliteration or shallowing of the mucobuccal folds.

Skin sclerosis is often treated with D-penicillamine, a chelating agent that affects unknown mechanisms of collagen formation. Experimental drugs, such as interferon-gamma and cyclophosphamide, and photophoresis have been used with varying degrees of success.

Management of the systemic effects of this disease is not well established, although some large uncontrolled series suggest that D-penicillamine has beneficial effects (Stone &Wigley, 1998). Interferon-gamma is effective, but its use is limited because of inflammatory sequelae.

2.2 Holoprosencephaly

Holoprosencephaly is considered as the most frequent anatomical central nervous system defect in humans (Orioli & Castilla, 2010). However, relatively few epidemiological studies have been performed on holoprosencephaly at older gestational ages, and no definitive risk factor has been clearly proved to be associated with holoprosencephaly. (Orioli & Castilla, 2010). Holoprosencephaly occurs when the prosencephalon fails to cleave sagittally into cerebral hemispheres, transversely into telecephalon and diencephalon, and/or horizontally into olfactory and optic bulbs. Nevertheless, substantial variations of the cerebral defect, as ell as of the accompanying facial anomalies, exist, generating differences in the ascertainment of the involved cases. Severe ear defects, as well as microstomia, were part of the spectrum of the condition. Several studies have excluded, or analyzed separately, the holoprosencephaly cases with chromosome abnormalities, and/or with recognized monogenic syndromes. The chromosome status of a holoprosencephaly patient is not easy to determine, due to their high perinatal mortality rate, and at least 10% of those with normal karyotypes have microdeletions/duplications and remain undetected by usual karyotyping (Orioli & Castilla, 2010; Mastroiacovo et al., 1995).

(Orioli & Castilla, 2010) determined whether craniofacial and noncraniofacial defects in holoprosencephaly cases. They confirmed the observation of Mastroiacovo et al., that among craniofacial defects, severe ear anomalies with atresia of the auditory canal, as well as microstomia, were part of the spectrum of holoprosencephaly (Mastroiacovo et al., 1995). Of the noncraniofacial defects, 24% of the holoprosencephaly cases had genital anomalies, 8% postaxial polydactyly, 5% vertebral defects, 4% limb reduction defects, and 4% had transposition of great arteries; all these defects were significantly associated with holoprosencephaly, while no significant association was found between holoprosencephaly and anencephaly, spina bifida, or encephalocele (Orioli & Castilla, 2010)..

2.3 Richieri-Costa–Pereira syndrome

In 1992 Richieri-Costa and Pereira (Richieri-Costa &Pereira, 1992) described a new syndrome of acrofacial dysostosis, in five unrelated Brazilian females, characterized mainly by Robin sequence, cleft mandible, and limb defects (Favaro et al., 2010). The family history showed parental consanguinity, recurrence in sibs, and increased death rate in males, which led the authors to suggest that this new condition was caused by an autosomal recessive gene(Favaro et al., 2010). Subsequently, the same authors described the first males with this condition (Favaro et al., 2010). The causative gene of this syndrome remains unknown and molecular investigations are in progress. Favaro et al stated the main features and prevalence of this syndrome as follows: microstomia (100%), micrognathia (100%), clinical or radiological abnormal fusion of the mandible (100%), cleft palate/Robin sequence (78.5%), absent central lower incisors (80%), minor ears anomalies (92.8%), hypoplastic thumbs (96.2%), hypoplastic thenar/hypothenar region (83.3%), mesomelic shortening of upper (51.8%) and lower limbs (88.8%), hypoplastic halluces (92.5%), and clubfeet (100%) (Favaro et al., 2010).. Language assessment showed learning disability in 14 cases (84%), and language disorder in 15 (77%). Favaro et al suggested that, due to the high frequency of

airway obstruction and feeding difficulties which are common findings in infancy, corroborate that individuals with Richieri-Costa–Pereira syndrome need special support, mainly in first years of life when most of the deaths occur (Favaro et al., 2010).

2.4 Freeman–Sheldon syndrome

Freeman–Sheldon syndrome, also known as distal arthrogryposis, type 2a; OMIM #193700, was first described by Freeman and J.H. Sheldon in 1938 (Corrigan et al., 2006). In 1975, Antley et al introduced the term 'whistling face syndrome' for the condition (Antley et al., 1975). Freeman–Sheldon syndrome is a heterogeneous condition both in its presentation and in its mode of transmission and both sexes are equally affected Freeman–Sheldon is an uncommon, morphologically well-defined syndrome. Orofacial findings of the condition are: A distinctive facial appearance of microstomia, microglossia, a short nose, long philtrum, H-shaped chin dimple, and sunken eyes is described. Extracranially, anomalies of the long bones, scoliosis, hand abnormalities, and joint contractures are found in most of the cases. The syndrome has also been termed 'Windmill–Vane hand' and although rare, is one of the commonest causes of multiple inherited congenital joint contractures(Corrigan et al., 2006). Intelligence is usually normal, although mental disability have been also reported in some cases [4–6]. Congenital respiratory system abnormalities and microstomia related feeding problems have been documented in a number of cases (Song et al., 1996; Corrigan et al., 2006; Antley et al., 1975). Presentation of complications in adolescence has also been reported. Song *et al*. described a 13-year-old with Freeman–Sheldon syndrome who developed late-onset dysphagia and subsequent weight loss. Corrigan et al reported the dental management experience in a patient with Freeman–Sheldon syndrome (Corrigan et al., 2006).

Ohyama *et al*. presented a case in which a mouth expander was used as a nonsurgical method of correcting microstomia (Ohyama et al., 1997). The authors claimed that this therapy produced an increase in mouth width. Corrigan et al suggested that it is debatable whether this change was actually induced by mouth expander use or whether it was simply a result of normal facial growth (Corrigan et al., 2006). No other interventions to improve microstomia have been reported in relation to Freeman– Sheldon syndrome yet.

2.5 De novo duplication of maternal origin of the 15q11.2-q14 pws/ as region [46, xx, dup (15) (q11.2-q14)]

The 15q11-q13 PWS/AS critical region involves genes that are characterized by genomic rearrangements, including interstitial deletions, duplications, and triplications (Browne et al., 1995). Multiple repeat elements within the region mediate rearrangements, including interstitial duplications, interstitial triplications, and supernumerary isodicentric marker chromosomes, as well as the deletions that cause Prader–Willi syndrome and Angelman syndrome. Recently, duplications of maternal origin concerning the same critical region have been implicated in autism spectrum disorders (Kitsiou-Tzeli et al., 2010) presented a 6-month-old girl with a de novo duplication of maternal origin of the 15q11.2-q14 PWS/AS region (17.73Mb in size) [46,XX,dup(15)(q11.2-q14)] detected with a high-resolution microarray-based comparative genomic hybridization (array-CGH) Kitsiou-Tzeli et al., 2010 The features of the condition were described by the same authors as: severe hypotonia, obesity, microstomia, long eyelashes, hirsutism, microretrognathia, short nose, severe

psychomotor retardation, and multiple episodes of drug-resistant epileptic seizures, partial corpus callosum dysplasia documented via magnetic resonance imaging. The duplicated region was quite large extending beyond the Prader–Willi–Angelman critical region, containing a number of genes that have been shown to be involved in autism spectrum disorders, exhibiting a severe phenotype, beyond the typical PWS/AS clinical manifestations. Reporting of similar well-characterized clinical cases with clearly delineated breakpoints of the duplicated region will clarify the contribution of specific genes to the phenotype (Kitsiou-Tzeli et al., 2010).

2.6 Hallerman – Streiff syndrome

Hallerman - Streiff syndrome or Francois Syndrome also known as oculomandibulodyscephaly with hypotrichosis was first described by Aubry in 1893. The syndrome was later defined as Hallermann-Streiff Syndrome, underlining the differences with regard to Franceschetti's mandibulofacial dysostosis (Cannistrà et al., 1999).

All individuals with Hallermann- Streiff syndrome have been sporadic, without a sex predilection, but inheritance pattern is still debated (Pizzuti et al., 2004). Concordant monozygotic twins have been described (Van Balen, 1961) and the few cases of Hallermann-Streiff syndrome with children always had unaffected offspring (Hendrix& Sauer, 1991).Oculodentodigital dysplasia is a genetic disorder related to dominant mutations in the connexin 43 gene at chromosome 6q22-23 (Paznekas et al., 2003). Spaepen et al suggested that several clinical features of this autosomal dominant highly penetrant disorder overlap those of the Hallermann- Streiff syndrome (Spaepen et al., 1991). Due to the clinical overlap between Oculodentodigital dysplasia and Hallermann- Streiff syndrome Pizzuti et al tested the work hypothesis they could be allelic disorders, both caused by GJA1 gene mutations and stated that the Homozygous GJA1 Gene Mutation Causes a Hallermann-Streiff/ Oculodentodigital dysplasia Spectrum Phenotype.Hallermann in 1948 and Streiff in 1950 described the cardinal features of the condition as: dyscephaly with bird facies, frontal or parietal bossing, dehiscence of sutures with open fontanelles, hypotrichosis of scalp, eyebrows and eyelashes, cutaneous atrophy of scalp and nose, mandibular hypoplasia, forward displacement of temporomandibular joints, high arched palate, small mouth, multiple dental anomalies and proportionate small stature (Hoefnagel & Benirschke, 1965). Defraia et al assessed the following features from a dentoskeletal point of view: aplasia of the anterior teeth, skeletal Class II malocclusion, narrow upper arch, bilateral posterior crossbite, and anterior open bite (Defraia et al., 2003). Ophthalmic features of the condition are microphthalmia, congenital cataracts, blue sclerae and nystagmus. Individuals with Hallermann-Streiff Syndrome, presence of mandibular hypoplasia and microstomia can result in difficult intubation. Recognition of this syndrome should alert the physician to the possibility of difficulty in airway maintenance (Malde et al., 1994).

2.7 Hutchinson–Gilford progeria

Hutchinson-Gilford progeria syndrome (OMIM 176670) first described by the general practitioner Jonathan Hutchinson in 1886, is a very rare autosomal dominant disorder characterised by growth retardation and progressive, premature senescent changes of the skin, bones and cardiovascular system (Sevenants et al., 2005). According to Polex and Hegele, since 1886 fewer than 100 cases of Hutchinson-Gilford progeria syndrome have been reported, with approximately 40 cases currently diagnosed (Polex & Hegele, 2004).

Feature	Frequency
Prenatal growth delay	0-25 %
Postnatal growth delay	75-100 %
Normal skull growth	50-75 %
Cognitive development	75-100 %
Hair sparse/alopecia	75-100 %
Increased visibility vessels	
Cranium	75-100 %
Nasal bridge	75-100 %
Prominent forehead	25-50 %
Absent eyebrows/eyelashes	50-75 %
Small face	75-100 %
Thin nasal skin	75-100 %
Convex nasal profile	25-50 %
Crowded teeth	50-75 %
Increased dental decay	50-75 %
Absent ear lobule	25-50 %
High voice	75-100 %
Lipodystrophy	75-100 %
Narrow upper thorax	75-100 %
Prominent abdomen	75-100 %
Broadened finger tips	50-75 %
Nail dystrophy	50-75 %
Horse riding stance	50-75 %
Decreased mobility	
Elbows	75-100 %
Wrists	25-50 %
Fingers	75-100 %
Hips	75-100 %
Knees	75-100 %
Ankles	25-50 %

Table 3. Major Findings in 142 Patients With Hutchinson–Gilford Progeria Syndrome (adopted from Domingo et al, 2009)

Fong stated that, most cases are caused by a de novo single-nucleotide substitution in codon 608 of prelamin A (p.G608G (GGC>GGT), p.G608S (GGC>AGC)), leading to the mutated Hutchinson-Gilford progeria syndrome gene product lamin A (LMNA), a structural component of the nuclear membrane (Fong & Meta, 2004). Lamin A contributes to nuclear

structural integrity and chromatin regulatory mechanisms (Martin, 2005). Progerin is the mutant form of lamin A and while progerin is expressed at very low levels normally, it is expressed at much greater levels in Hutchinson-Gilford progeria syndrome (Domingo et al, 2009). According to Domingo et al, Progerin accumulation in cells has been associated with instability of the nuclear membrane, progressive nuclear damage, and premature cell death. Polex and Hegele have shown structural nuclear abnormalities in 48% of Hutchinson-Gilford progeria syndrome fibroblast nuclei compared with less than 6% of normal control cells (Domingo et al, 2009). Furthermore, they stated that, Hutchinson-Gilford progeria syndrome fibroblasts undergo hyperproliferation followed by rapid apoptosis.

From the Greek geras, meaning _old age,' progeria is a human disease model of accelerated senescence (Domingo et al, 2009). Affected individuals typically appear normal at birth but begin to demonstrate features of accelerated aging within the first year of life.

Clinically, the main features of Hutchinson-Gilford progeria syndrome include alterations in skin, bone, and cardiovascular tissues, marked retardation of growth, loss of subcutaneous fat, and distinctive bone changes. These main features and their prevalances were shown in Table 3.

Although, microstomia was not reported in majority of the cases, however, sclerodermatous changes which could be the first manifestation of Hutchinson-Gilford progeria syndrome, can result in restriction of the oral aperture.

Among individuals with Hutchinson-Gilford progeria syndrome, death occurs at 13 years of age, most commonly from progressive coronary and cardiovascular atherosclerosis (Pollex&Hegele, 2004).

2.8 Burton skeletal dysplasia

Burton skeletal dysplasia was first described by Burton et al in 1986 (Burton et al., 1986). They reported a pair of sibs suffering from a new skeletal dysplasia with clinical and radiological findings similar to those of Kniest dysplasia but with important differences. They reported the main clinical findings as: sibs with short stature, bowing and shortness of limbs, enlargement of wrists and knee joints, stiffness of knee joints, and a bell-shaped thorax with flare of lower ribs. In addition, they had a small mouth with pursed lips, downward dislocation of the lenses, and myopia. In agreement with Burton et al, Lo et al added the third case to he literature and reported also a small mouth with pursed lips that remained more or less the same size whether she laughed or cried, and a deep philtrum (Lo et al., 1998).

2.9 Fine–Lubinsky syndrome

In 1983, Drs. Fine and Lubinsky described a single patient with craniofacial anomalies, hearing loss, cataracts, microstomia, and developmental delay (Fine & Lubinsky, 1983). In following reports, the main clinical features of the condition was described as: craniosynostosis, prominent frontal bones, flat facial profiles, small noses, microstomia, hearing loss, developmental delay, and abnormal digits (Preus et al., 1984; Suthers et al., 1993; Ayme´ & Philip, 1996; Holder et al., 2007; Schoner et al., 2008; Cole et al., 2010).

Schoner et al reported a female fetus of 24 weeks gestational age with Fine-Lubinsky syndrome and based the diagnosis of Fine-Lubinsky syndrome on growth deficiency,

brachycephaly, flat face with associated dysmorphic signs, microstomia and cataract (Schoner et al., 2008).
Cole performed a G-banded chromosome analysis, telomere FISH study, and an array based comparative genome hybridization analysis in a patient with Fine-Lubinsky syndrome (Cole et al., 2010). The genetic evaluation of the individual revealed no abnormalities. However, Holder et al described the first brother and sister sibling pair with features suggestive of Fine– Lubinsky syndrome and the identification of a brother–sister sibling pair with unaffected parents suggested a possible autosomal recessive inheritance pattern with a 25% recurrence risk to future siblings (Holder et al., 2007).

2.10 Leopard syndrome

LEOPARD syndrome, also known as Multiple Lentigines syndrome, Cardio-cutaneous syndrome, Moynahan syndrome, Lentiginosis profusa and Progressive Cardiomyopathic Lentiginosis is a polymalformative disease affecting many organs and systems and was first described by Zeisler and Becker in 1936 (Zeisler& Becker, 1936).
The abnormalities related to Leopard syndrome are: Electrocardiographic anomalies, ocular hypertelorism, pulmonary stenosis. anomalies of genitalia, retardation of growth and deafness(Yam et al., 2001).
The Leopard syndrome follows an autosomal dominant mode of transmission with a wide variability in expression (Ho et al., 1989). However, according to some authors, the syndrome may arise as a result of a spontaneous mutation. Microstomia associated with Leopard syndrome was reported by Yam et al. According to Sarkozy et al, Leopard syndrome may be sporadic or inherited as an autosomal dominant fully penetrant trait (Sarkozy, et., 2008). In approximately 85% of the patients with a definite diagnosis of Leopard syndrome, a missense mutation is found in the *PTPN11* gene, located on chromosome 12q24.1 (Diglio et al., 2002; Sarkozy et al., 2004).

2.11 Auriculo-condylar syndrome

Auriculo-condylar syndrome (OMIM 602483) was first described by Jampol et al in 1998 (Jampol et al., 1998). It is an autosomal dominant disorder of first and second pharyngeal arches, is characterized by malformed ears, prominent cheeks, microstomia, abnormal temporomandibular joint, and mandibular condyle hypoplasia. Comparison of clinical signs of patients with auriculo-condylar syndrome from previous reports were shown in Table IV. Treacher Collins syndrome (OMIM 154500), oculoauriculo- vertebral spectrum (OMIM 164210), and Townes–Brocks syndrome (07480) have several overlapping clinical signs with auriculo-conylar syndrome and should be considered for differential diagnosis of the condition. Masotti et al. (Masotti et al., 2008) stated that, the mapping and identification will certainly bring important contributions to the understanding of the development of embryonic structures derived from these pharyngeal arches, as well as to perform differential diagnosis.
The auriculo-condylar syndrome gene is still unknown. The intra- and inter-familial phenotypic variation in auriculo-condylar syndrome has been noted by several authors. (Guion-Almeida et al., 1999; Storm et al., 2005; Masotti et al., 2008; Jampol et al.,1998) Masotti et al have performed a wide genome search and observed evidence of linkage to 1p21.1–q23.3. They have also stated that an evidence for genetic heterogeneity. (Masotti et al., 2008)

Clinical signs	Cases	Frequency(%)
TMJ abnormality	26/26	100
Micrognathia	33/46	71.7
Microstomia	26/42	61.9
Stenotic ear canals	6/17	35.3
Mild developmental delay	3/13	23.1
Abnormal palate	14/29	48.2
Glossoptosis	11/22	50.0
Ptosis	3/11	27.3
Feeding difficulties	8/30	26.7
Prominent cheeks	29/43	67.4
Respiratory distress	14/34	41.2
Macrocephaly	3/12	25.0
Hearing loss	12/27	44.4
Ear constriction	46/47	97.9

Table 4. Clinical signs and the prevalances of Auriculo- condylar syndrome from previous reports (adopted from Masotti et al., 2008)

2.12 Chromosome 22q11.2 Deletion syndrome (Velocardiofacial/DiGeorge syndrome)

Dr. Angelo DiGeorge described a group of infants with congenital absence of the thymus and parathyroid glands In 1965 (DiGeorge et al., 1965). Facial dysmorphia, conotruncal cardiac malformations, and speech delay were included in the spectrum and various other names came to be applied to this constellation of phenotypic features, including velocardiofacial syndrome, cardiofacial syndrome, and conotruncal anomaly face syndrome(McDonald-McGinn & Sullivan, 2011). Major phenotypic features of the condition were listed in Table 5. According to the review of McDonald-McGinn and Sullivan, the estimated prevalence has been cited as being 1:3000-1:6000 births (McDonald-McGinn & Sullivan, 2011).

Major Phenotypic Features
Cardiac anomaly
Tetralogy of Fallot
Ventriculoseptal defect
Interrupted aortic arch
Truncus arteriosus
Vascular ring
Immune deficiency
T-cell lymphopenia
Thymic aplasia with absent T cells
Delayed IgG production
Palatal defects
Velopharyngeal insufficiency
Submucous cleft palate
Overt cleft palate
Cleft lip and palate

Table 5. Major phenotypic features of Chromosome 22q11.2 Deletion Syndrome (adopted from McDonald-McGinn & Sullivan, 2011)

Cytogenetic and molecular studies have showed that most patients with DiGeorge/ Velocardiofacial syndrome have interstitial or submicroscopic deletions within 22q11 (Driscoll et al., 1992) Clinical findings in Chromosome 22q11.2 Deletion syndrome were shown in Table 6.

Clinical findings
Feeding difficulties
Respiratory infections
Developmental delay
Short stature
Long face, vertical maxillary excess
Abundant hair
Mild, upslanting palpebal fissures
High, wide nasal bridge
Prominent middle nose
with hypoplastic nasal alae
Philtrum anomalies
Microstomia
Long recessed chin
Abnormal ears
Short, broad neck
Scoliosis
Heart defect
Umbilical hernia

Table 6. Clinical findings in Velocardiofacial syndrome (adopted from Jaquez et al., 1997)

Microstomia was reported to be one of the clinical findings in Chromosome 22q11.2 Deletion Syndrome. (Jaquez et al., 1997, Martin Mateos et al., 2000) However, the pathogenesis and the frequency of microstomia among individuals with Chromosome 22q11.2 Deletion Syndrome are not known.

2.13 Epidermolysis bullosa

Epidermolysis bullosa is a group of rare, genetically determined disease, which is characterized by cutaneous and mucosal blistering associated with occasional subsequent scarring secondary to minor trauma. It is divided into 3 major types by histological findings, and includes approximately 23 variants, manifested by a spectrum of clinical presentations (Stavropoulos% Abramovicz, 2008; Ozgur et al., 2005).The diagnosis is confirmed by examining the basal membrane with transmission electron microscopy, immunohistochemical analysis, and complementary examinations, such as optical microscopy, immunofluorescence, and enzymatic analysis (Siqueira et al., 2008).

The condition affects approximately 1 in 50,000 to 1 in 500,000 births and encompasses a group of congenital chronic noninflammatory skin disorders. Their common primary

feature is the formation of blisters and erosions at the site of minor mechanical trauma in the skin, mucocutaneous layers of the oral mucosa, and respiratory and digestive tracts (Ergun et al., 1992; Marx&Stern, 2003).

Results of the first gene therapy was reported in 2006 by De Luca and colleagues on a patient with generalized junctional epidermolysis bullosa who had compound heterozygous mutations in the β3 chain of laminin 332 (Fine, 2010) .

Most of the more severe subtypes are associated with clinically significant extracutaneous complications. Some subtypes may lead to death, even in early infancy. Dystrophic epidemolysis bullosa has either an autosomal- dominant or recessive pattern of inheritance and is associated with loss of fibrils of anchorage and increased collagen disintegration on the superficial dermis due to excessive synthesis of collagenase (Silva et al., 2004; de Freitas, 1986). This characteristic may results in limited mouth opening. The recessive subtype of the condition is the more severe form, in which the continuous formation of cicatricial tissue, especially in the hands and feet, leads to the joining of the fingers and toes. The dominant form of epidermolysis bullose presents with bullous eruptions that develop after trauma and heal leaving atrophic scars and milium, which are small white nodules that appear beneath the scars.

According to Stavropoulos and Abramovicz (Stavropoulos& Abramovicz, 2008). oral involvement of epidermolysis bullosa may includes occasional intraoral blistering that heals rapidly and patients may present with severe intraoral blistering and subsequent scar formation which results in restriction of the mouth opening. Spinocellular carcinoma is the most frequent complication of epidermolysis bullosa and morbidity and mortality were frequently reported. (Liversidge et al., 2005).

3. Treatment of Microstomia

The main goal and objective of microstomia treatment are: the reconstruction of the orbicularis sphincter for adequate lip functioning, obtaining lip symmetry and formation of well positioned and undistorted scars. The cause and severity of the perioral restriction and esthetic and functional requirements influence the treatment selection and procedures. Several techniques have been described for the reconstruction of the labial commissures. Surgical possibilities include z-plasties, skin grafts, commissurotomies and local flaps. In addition, a number of nonsurgical methods and designs have been used for maintaining adequate mouth opening. Individuals with restricted mouth opening were considered to be good candidates for intra- and extraoral stretching devices, static and dynamic oral appliances and sectional and collapsible dentures (Wust, 2006).

3.1 Surgical therapy

Basically, an effective surgical treatment for individuals with microstomia must solve two problems: first, to restore the oral opening size by releasing the commissural contracture; and second, to minimize the cosmetic defect caused by oral angle deformation (Griskevich, 2010). Restoration of the oral commissure is always a difficult procedure related to the complex functional and esthetic entity of the circumoral region. idely used methods usually consist of scar 'excision' in the oral angle zone and wound closure with mobilised mucosal flaps (Griskevich, 2010). Dieffenbach.(Dieffenbach, 1829; Jaminet et al., 2009) presented the first technique to correct microstomia by performing advancement of superior, inferior, and

lateral mucosal flaps to reconstruct the corner of the mouth after removal of a triangular wedge of scar tissue. The procedure was modified later by Converse (Converse, 1959; Jaminet et al., 2009) and later by Mehra et al (Mehra et al., 1998; Jaminet et al., 2009) by performing either a vermilion advancement or the transposition of the buccal mucosa following the commissurotomy procedure.

Gillies and Millard (Gillies & Millard, 1957, Jaminet et al., 2009) used a vermilion flap to reconstruct the upper lip and an oral mucosal advancement flap for the lower lip. Villoria (Villoria, 1972) transposed inner and outer orbicularis oris muscle flaps and performed an advancement of the oral mucosa to reshape the vermilion. Johns et al (Johns et al., 1998;Jaminet et al., 2009) suggested the success of the triangular pedicled flap for oral commissuroplasty, with good result. Muhlbauer (Muhlbauer, 1970; Jaminet et al., 2009) proposed 2 Z-plasties, using the rotation of 2 small skin flaps into the mucosa of the lip. However, this technique is rarely used as it does not allow restoration of the oral angle if the scars are rough. Sorensen pointed out, ''Traditionally, defects are usually closed with a Y-V plasty, but in my opinion the classical Z-plasty is better (Sorensen, 1979).'' (Griskevich, 2010). Fairbanks and Dingman reconstructed the oral aperture by obliquely dividing the existing vermilion into 2 diminishing flaps approximated to the new mouth angle (Fairbanks&Dingman, 1972). After contracture release, a trilobed flap is created from the mucosa that is advanced over the defect and sutured into place; the middle part of the flap is used to create the vertical part of the commissure; an overcorrection (2–4 mm) is advisable and a splint is recommended to prevent recurrence of the contracture. After triangular scar excision, mucosal advance- ment Y–V flap, or mucosal rhomboid flaps per side or skin grafts are used (Griskevich, 2010). Takato et al used a free forearm flap for reconstruction of the oral cavity and vermilion flaps at the oral commissure on a patient with severely constricted oral cavity because of mucosal adhesions (Takato et al., 1989). Martins et al reconstructed corners of the mouth via 4 rhomboid flaps rotated from the buccal mucosa (Martins et al., 2003). Ayhan et al described a new technique of reconstructing with a composite graft of the ear-lobule to surgically correct microstomia (Ayhan et al., 2006). Composite auricular lobule grafts, triangular pedicle flaps and bipedicled deep inferior epigastric perforator flaps are seldom used for the reconstruction of the oral commissure.

With the knowledge of the literature review, it can be stated that, no commissure reconstruction without scars of operation has been achieved so far by using the available techniques. Griskevich suggested that most of the commissuroplasties cannot bring good cosmetic results as flaps possess different qualities and the transposition of the flap inwards and placing it within the mucosa deforms the oral angle. For commisurotomy, the red mucosal flap is turned out for wound closure, creating a new angle deformation similar to mucosal ectropion. The oral angle zone becomes deeper, more rounded and wider; the red mucosa remains visible when the mouth is closed, which creates a cosmetic defect. Moreover, the end of the advanced mucosal flap was tightened with sutures, which could impair blood circulation, and it could result in microstomia recurrence. Therefore, an overcorrection and a splint are often recommended after all of microstomia operations (Griskevich, 2010). According to the same author, all techniques mentioned above can provide satisfactory functional outcomes, but the 'aesthetic' results were found only ''acceptable (Griskevich, 2010).

The need for a detailed description of anatomical features in their relation to red mucosa after surgery in the newly commissural region still remains. (Griskevich, 2010).

3.2 Non surgical therapy

Compression therapy, mouth splinting, scar massage, contact media, exercise, patient education and neck splinting are standard treatments for the prevention and management of microstomia (Wust, 2006). It has been demonstrated that, effective contracture management needs to provide horizontal, vertical, and circumferential lip stretch.

3.2.1 Static and dynamic mouth splints

Basically, two forms of functional splinting devices exist: passive splints which prevent contraction, and dynamic widening devices which regain lost oral opening. These may be retained by intraoral (fixed or removable) or extraoral devices. The removable splint usually resembles a mouthguard made of acrylic resin and is retained with clasps. The fixed appliance is retained on orthodontic bands placed on the primary maxillary second molars and central incisors. Both devices support acrylic resin posts that maintain the commissural regions equidistant to the midline. Reisberg et al. recommended using an extraoral commissure conformer attached to an orthodontic headgear strap (Reisberg et al., 1983). The amount of tension needed is based on the distance from the midline to the unaffected side when the patient smiles broadly. Many investigators have documented the use of lip and cheek retractors as a splinting device. Silverglade and Ruberg stated that an expansile removable appliance to regain lost lateral dimension due to scar contracture is usefull (Silverglade.& Ruberg, 1986) Two acrylic phalanges are connected to an orthodontic palatal expanding device that expands 0.25 mm with each adjustment. Madjar et al. described a commissure widening device in which a stainless steel wire is bent into the shape of an **fl** and fitted with acrylic resin lip holders such that force is directed laterally and distally (Madjar et al., 1987). Conine et al. evaluated the structural and clinical characteristics of major microstomia orthoses and proposed the Vancouver microstomia orthosis (Conine et al., 1989). They stated an average of 7 mm in the horizontal and 13 mm in the vertical active range of motion within 9 weeks of use.

Dynamic Mouth Splint designed by Van Straten, was considered for trial to improve vertical mouth opening (van Straten, 1991). However, some difficulties were identified. These included:

1. *the thermoplastic material was not designed for intra-oral use,*
2. *the risk of damage to dental structures caused by lack of conformity to the teeth,*
3. *the risk of oral infection caused by possible microbial contamination of the splint lining,*
4. *the fact that the application requires a vertical mouth opening of more than 25 mm.*

Subsequently, a Modified Dynamic Mouth Splint was developed that combines design features of the original Dynamic Mouth Splint with materials designed for intra oral use (Wust, 2006). Wust stated that, good results in functional mouth opening can be obtained by using the Modified Dynamic Mouth Splints (Wust, 2006).

3.2.2 Vertical orthosis

Microstomia devices have been developed to decrease the scarring and contractures imposed by the healing process. Many of these devices are useful for the control of horizontal mouth opening restriction. Recently, another Davis proposed an effective, simple, economical, orthotic device for the enlargement of the vertical mouth diameter and suggested that, patients gave positive feedback for comfort and ease of use, with increased mouth mobility and range of motion (Davis et al., 2006). Additionally, it has been suggested

that, from a visual assessment, the vertical orthoses are more comfortable to wear for an extended period because the patient can swallow and, with the lip-based device, talk while it is in place.

3.2.3 Sectional dentures

Without surgical operation it is very difficult to perform prosthetic treatment for patients with microstomia, especially when the severe restriction of the mouth circumference length . Because the smallest diameter of a fully retentive denture and a impression tray may be larger than the greatest diameter of the mouth opening, a sectional impression tray and a sectional denture may be indicated (Suzuki et al., 2000).

Yenisey et al described a technique for the fabrication of mandibular and maxillary sectional trays and a sectional mandibular complete denture fabrication for a patient with microstomia induced by scleroderma a sectional mandibular denture was a suitable treatment to resolve the problem of microstomia caused by scleroderma. They stated that, the cast hinge design reduced the overall costs and simplified the laboratory technique. This technique has proven to be simple, inexpensive and applicable to selected microstomic patients (Yenisey et al., 2005). Watanabe et al reported the use of cast Fe-Pt magnetic attachments to treat an edentulous patient with microstomia induced by scleroderma (Watanabe et al., 2002) and described a cast iron-platinum magnetic attachment system applied to sectional collapsed complete denture. With the use of lingual and palatal midline hinges and an Fe-Pt magnetic attachment, the sectional collapsed complete dentures were successfully and easily inserted and continue to provide adequate function in the patient's mouth. Cura et al described an other technique used to fabricate mandibular and maxillary sectional trays and a folding maxillary complete denture for a patient with limited oral opening caused by systemic sclerosis. For the foldable denture, the anterior teeth had to be arranged on a second base and the hinge fitted at a location higher than the denture base (Cura et al., 2003).

3.3 Exercise programs

Pizzo et al assess the effects of a nonsurgical exercise program on the decreased mouth opening in a group of 10 systemic scleroderma patients with severe microstomia (maximal mouth opening ≤30 mm) (Pizzo et al., 2003). The subjects were instructed to perform an exercise program including both mouth-stretching and oral augmentation exercises. The effects of such exercises were assessed after an 18-week period by measuring the maximal mouth opening of each subject. The exercise program improved the mouth opening of all subjects without significant differences between dentate and edentulous ones. At the end of the 18-week period, all patients commented that eating, speaking and oral hygiene measures were easier. The edentulous subjects also experienced less difficulty inserting their own dentures. These findings suggest that regular application of the proposed exercise program may be useful in the management of microstomia in systemic scleroderma patients (Pizzo et al., 2003)

4. Conclusion

Individuals with microstomia would benefit from early referral to several medical services. Regular follow-up with targeted preventive advice is essential, in view of the potential for

disruption of facial growth, genetic disorder pattern and the anatomical limitations faced in providing oral care and restorative treatment in patients with microstomia. The improvement of mouth opening impacts on the patients' quality of life by enabling them to perform activities such as speech, eating, dental hygiene, expression, social interaction, and receiving general anaesthesia via intubation rather than requiring a prolonged tracheostomy. This improved functional performance also impacts positively on psychosocial well being. Management of microstomia is a critical area when treating a patient with burn injuries and should be a priority due to its impact on quality of life (Wust, 2006). Additionally, long-term documentation of such cases and multicentre audit will enhance our understanding and improve our future management of similar rare and interesting genetic disorders.

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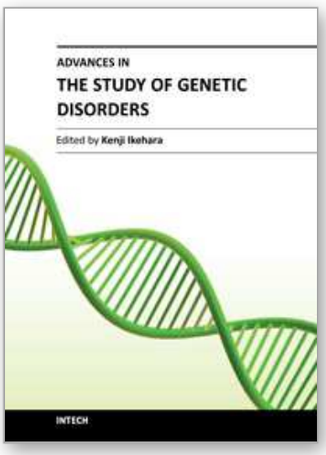
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Advances in the Study of Genetic Disorders

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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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