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GOLDENHAR SYNDROME WITH UNILATERAL TESSIER'S TYPE 7 CLEFT: REPORT OF AN UNCOMMON CASE

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ABSTRACT

Goldenhar syndrome, a variant of hemifacial microsomia, is a well-known developmental anomaly of maxillofacial skeleton that is apparent at birth. The first and second branchial arch involvement during early embryonic development results in a wide spectrum of anomalies that may include macrostomia and lateral facial clefts. Though clefts of the orofacial region are among the most common congenital facial defects, the occurrence of lateral facial clefts (Tessier's type 7 cleft) in Goldenhar syndrome is reported only in (5%) of the cases. The lateral facial cleft which results because of improper development of the perioral muscles of the face, gives an appearance of macrostomia giving rise to potential psychological, aesthetic and feeding problems. This clinical report throws light on an one year old male infant with Goldenhar's syndrome.

KEYWORDS: Goldenhar syndrome, Occuloauriculovertebral Syndrome, Maxillofacial, Ocular dermoid, Preauricular ear tags and Tessier's type 7 cleft.

INTRODUCTION

Goldenhar syndrome (GS) is a congenital disease first described in 1952 by ophthalmologist Maurice Goldenhar. In the literature, we can find many other synonyms of this defect

including oculo-auriculo-vertebral syndrome (OAVS), facio-auriculo-vertebral syndrome or Goldenhar Gorlin syndrome.[1,2] It is characterized by impaired development of structures such as eyes, ears (with or without hearing loss), lip, tongue, palate, mandible, maxilla and deformations of the teeth structures, because these parts of the face are derived from branchial arches, and it is also classified as 1st and 2nd branchial arch syndrome. In this syndrome, abnormalities localize in the internal organs such as heart, kidneys, in the central nervous system or in the skeleton and different vertebral defects are observed.[2,6] According to some authors for this reason other name like hemi facial microsomia shouldn't be used interchangeably while referring to this syndrome. Various studies have shown that this defect occur from 1:3500 or 1:5600 to 1:45 000 live births.[1,2,9,10]

The spectrum of GS abnormalities ranges from mild to severe ones and include patients with barely noticeable facial asymmetry to very pronounced facial defects (resulting from unilateral facial skeleton hypoplasia to facial clefts) with more or less severe abnormalities of internal organs and/or skeleton. The symptoms observed in this syndrome can be divided into groups according to the part of the body they affect,[11] and are presented in Table 1. The most common symptoms of GS are epibulbar dermoids or lipodermoids, dacryocystitis, auricular abnormalities, preauricular appendages, preauricular fistulas and hypoplasia of the malar bones, mandible, maxilla and zygomatic arch,[2,32] Children with GS may also present with low height, delayed psychomotor development, retardation (more frequently seen with cerebral developmental anomalies and microphthalmia), speech disorders (articulation disorders, rhinolalia, different voice disorders, unusual timbre), psycho-social problems, autistic behaviours,[3,33-35]

CASE REPORT

An one year old male infant was brought to our Department of Oral Medicine and Radiology by his parents with complaints of abnormally small shape and size of the right sided ear, absence of the left sided ear and presence of multiple small soft tissue growths in front of the abnormally formed ear which were present since birth. On obtaining detailed history it was revealed that baby was born at full term (37 weeks) via normal delivery in a local hospital, with 3 ½ kg weight to a 21 year old mother and 34 year old father at gravida 2 para 2: Patient's mother recalled that the delivery was spontaneous with vertex presentation but uneventful with cord wound thrice around the baby's neck. Post natal evaluation revealed The heart rate and respiratory rate recorded after the birth was 126 beats/min and 46

breaths/min respectively, cry of the baby soon after the birth was normal. As poor suckling reflex was elicited by the baby, breast feeding was not initiated within an hour after birth. The infant was referred to the ENT surgeon on the second day of birth for auditory evaluation However, ENT evaluation done was inconclusive, second audiology screening was done 35 days after birth. USG abdomen, Neurosonogram and 2D echo was done on the fourth week to rule out renal, neural and cardiac anamolies. Infant had a three year old elder sibling who was apparently healthy. The parents were related with a history of remarkable consanguinity and the mother had no history of drug intake or trauma during her pregnancy. On general examination, the infant was found to have no systemic disease.

On extra oral examination of the right sided ear revealed presence of two separate tissue tags or appendages (figure- 3). One of the appendage was pedunculated roughly spherical in shape located in close proximity to the tragus of the ear which is approximately of size 0.8x0.6cm in size, another appendage was evident in the pre auricular region approximately located 1cm in front of the lobule of the ear which was spherical in shape approximately 0.8x1cm in its maximum dimension with a smooth surface, colour same as the adjacent skin. On palpation all the inspectory findings are confirmed the tissue tag was soft on palpation and non-tender.

On examination of the left sided infra temporal region there is evidence of malformation of the left sided ear, presenting as three irregularly shaped tissue appendages of varying sizes or tags evident in left ascending ramus region, (figure -4). Three tissue appendages were 0.5cm, 0.7cm and 2.2cm in size respectively with a smooth surface, colour same as the adjacent skin. On palpation all the inspectory findings are confirmed the tissue tags were soft on palpation and non- tender. There was no evidence of normal external auditory canal in the left side. The infant was moving his head in response to the sounds on the right side but non responsive to the sounds from left side. The sensory milestones were delayed whereas the motor milestones were normal.

On examination of the Eyes: There was a tissue covering the temporal fornix of the sclera at the junction of the upper and lower eyelid in corner close to the lateral canthus of both the eyes. (figure- 5) The infant exhibited normal blink reflexes and eye ball movements.

The facial form was euryprosopic, facial profile was convex with posterior facial divergence, and notable facial asymmetry was evident in the left lower jaw region. There was deflection of the mandible towards left side (figure-1). Shift in the midline evident when the infant tried

to smile (figure- 2) and lack of approximation at the of the left commissure evident (figure-6). On TMJ examination the left TMJ movements cannot be appreciated On Intra oral examination; Number of teeth present was 12.Erupting 54, 64, 74 and 84 was present 51, 52, 61, 62,71,72 ,81 and 82 were already erupted , with normal shape , colour and midline shift towards left side was observed. Correlating the history, clinical examination and diagnostic criteria all features were suggestive of Goldenhar syndrome with Tessier's type 7 unilateral transverse orofacial cleft. The most closest differential diagnosis was Treacher Collin's Syndrome but the presence of bilateral lipodermoids of the eyes, absence of calvarial deformities made us to rule out this condition.

Infant was subjected Computed Tomography of the head and neck (plain) which revealed Complete Aplasia of the left sided condyle, deficient mandibular ascending ramus of the left side and absence external auditory meatus. (figure- 7 and 8).

Excision of preauricular ear appendages, reconstruction of the left sided ear with costochondral graft was planned. Patient is currently under follow up with periodical ophthalmic, auditory and dental evaluation.

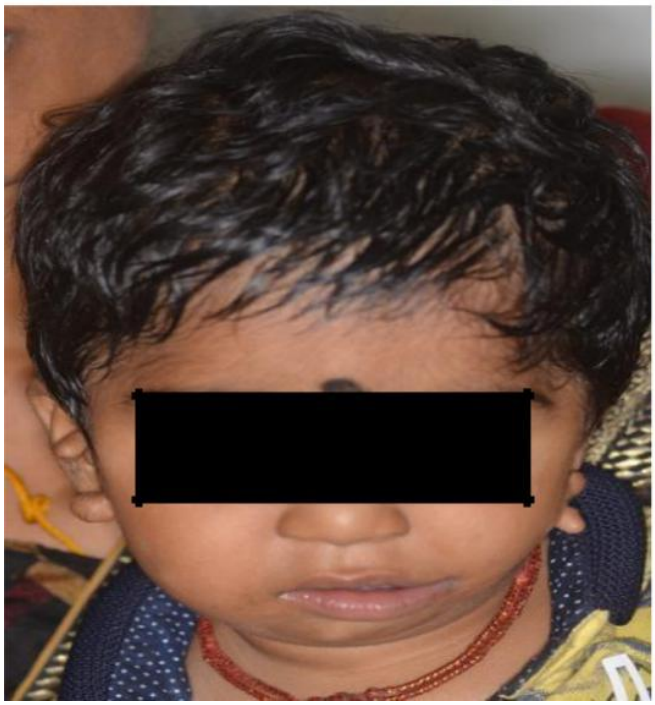


Figure 1: Profile.

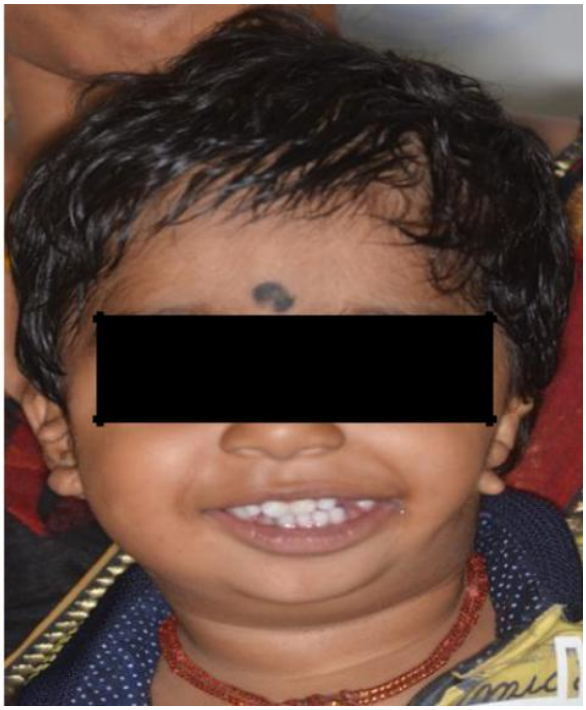


Figure. 2. Mandibular Hypoplasia (Left Side).

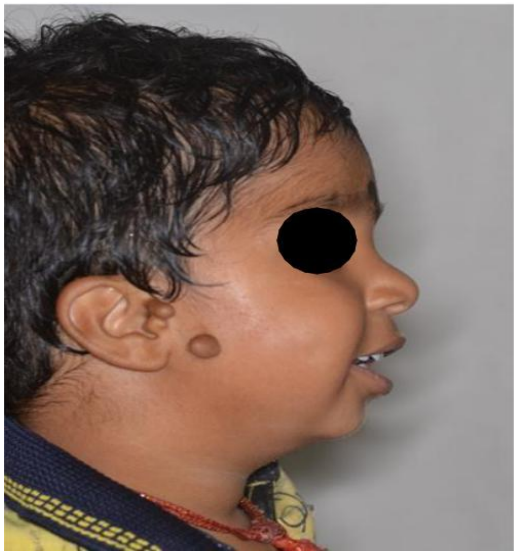


Figure 3: Preauricular Ear.

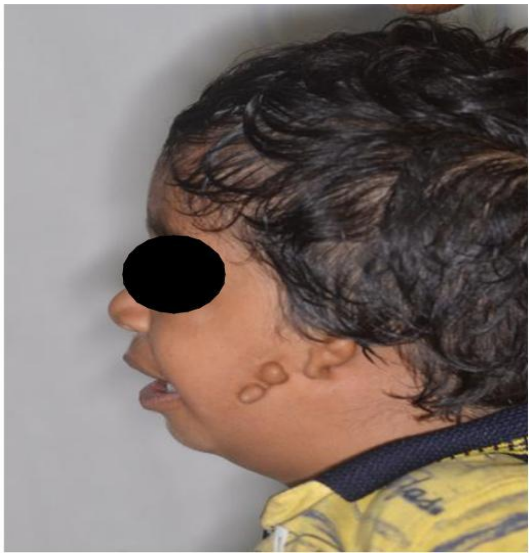


Figure 4: Anotia and Ear Appendages (Right side) Appendages (Left side).

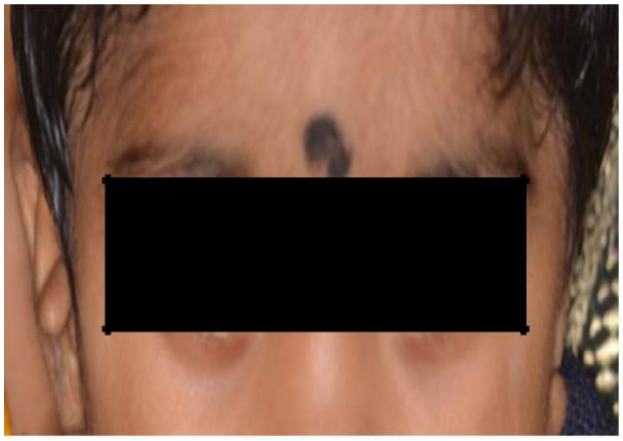


Figure 5: Eye Anomaly showing.

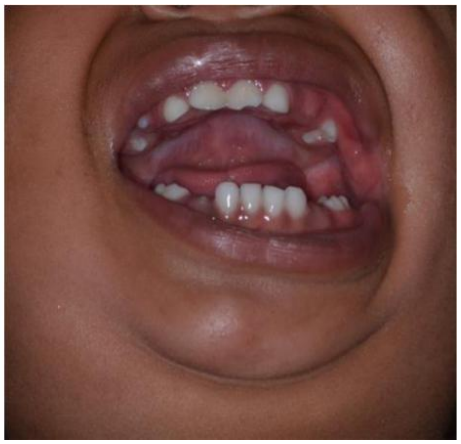
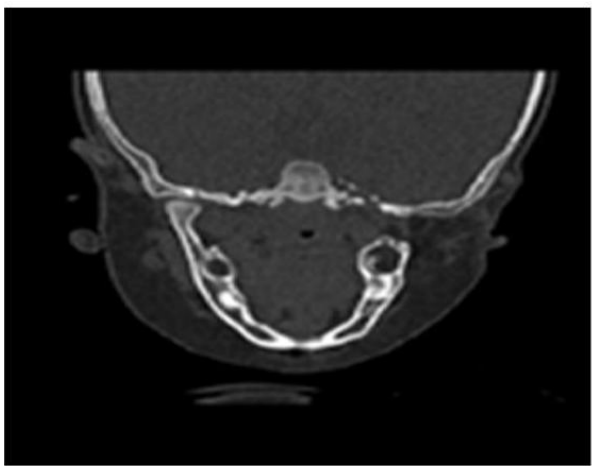


Figure 6: Transverse OroFacial Lipodermoids of both eyes cleft or Tessier's Type 7 Cleft.



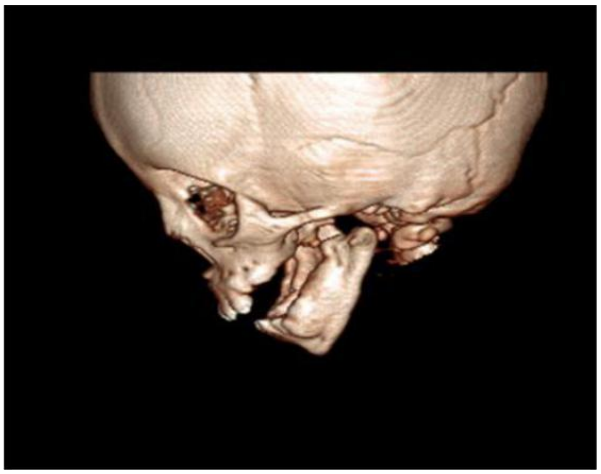


Figure 7: Coronal CT reveals Absence of Mandibular condyle. Figure 8: Reformatted CT view reveals Absence of External acoustic Meatus of the Left side and Deficiency of Ascending Ramus and Condyle.

Table 1: Anomalies associated with Goldenhar Syndrome.[2,11-31]

Dentofacial abnormalities	Unilateral facial hypoplasia **Facial bones** Prominent forehead,[17] Hypoplasia of the zygomatic area maxillary and mandibular Hypoplasia[18] **Mouth** Lateral facial cleft (unilateral macrostomia)[18] Facial paresis,[19] **Intraoral findings** Cleft lip, cleft palate, tongue cleft, unilateral tongue hypoplasia,[18] Gingival Hypertrophy,[18,19]
Salivary glands	Aplasia of parotid gland,[17]
Ear	Preauricular skin tags, fistulas and nodes,[17] Preauricular dimples to imperforated external acoustic meatus, deafness[20] Posteriorly angulated ears,[18,19] Pretragal anotia[22] Bilateral preauricular pits[22] Other external ear malformations - dysplasias and asymmetries Aplasias and atresias of the external meatus Middle and internal ear anomalies
Eye	Epibulbar dermoid (unilateral/bilateral)[22-23] Hypertelorism, ptosis[23,24] Small eye with notched upper lid,[24] short palpebral fissures, hypoplasia of supraorbital ridges[20,22] Prominent eyes with cloudy corneas[22] Juvenile glaucoma[25] Bilateral epicanthal folds[22] Lipodermoid (mostly bilateral)[26] Colobomas of the upper eyelid iris, choroidea and retina[27,28] Other eye anomalies Antimongoloid palpebral fissures Anophthalmia Cataract Blepharophimosis[29]
Vertebral column anomalies	Atlas occipitalization Synostosis. Hemivertebrae Fused vertebrae, Kyphoscoliosis Bifid spine[29] Butterfly vertebrae[20] Equinovarus deformity[19] Missing ribs Clinodactyly of the 5th fingers Short stubby fingers with ulnar deviation, hypoplastic distal phalanges. Club feet with prominent heel[22]

Other systemic abnormalities	Rib anomalies and anomalies of the extremities Congenital heart disease (ventricular septal defect, atrial septal defect, pulmonary stenosis)[29] Growth retardation, marked hair on body,[20] Torticollis,[30] upturned nose,[33] flat nasal bridge with broad nasal root,[32] deep creases on the feet,[33] Severe respiratory distress due to upper respiratory tract infection, tracheoesophageal fistulas,[19,22] Urogenital and gastrointestinal system: ectopic kidneys,[29] Uretropelvic junction obstruction, imperforate anus Central nervous system occipital encephalocele,[29] Anomalies of the larynx and lungs tracheoesophageal fistula Oesophageal atresia Retardation of mental development[29]

Etiopathogenesis of Goldenhar syndrome

Etiopathogenesis of GS is still very poorly known and in lot of cases remains unexplained. The reason of occurrence of this syndrome is multifactorial and dependent on genetic and environmental factors. In the literature, we can find information about cases running in the family with autosomal dominant as well as recessive inheritance.[15] According to Beleza Meireles et al,[1,4,14] there were authors who estimated the occurrence of patients with a positive family history of GS at the low percentage/level but others identified even 31% of familial cases. Some studies also show that first degree relatives were most often affected. and the risk of familial inheritance of this syndrome probably ranges between 2%-3%. Surprisingly most of the reported cases of this syndrome has a sporadic presentation.[5]

It is also noticeable that OAVS affects more male than female infants.[15,36&37] Among patients suffering from this condition, chromosomal abnormalities are often detected. The following abnormalities have been noted so far: deletion in 1p22.2-p31.1, 5q13.2, 5p15, 12p13.33, 14q31.1q31.3, 15q24.1, 22qter, deletions in 22q11.2, duplication in 10p14-p15,

14q23.1, 22q11.1-q11.21, trisomy 18, 22, partial trisomy of the 22q11 region, aneuploidies in chromosome X, translocation t(9;12) (p23;q12.2), inversion inv9(p11;q13), inv14(p11.2; q22.3), mosaicism of trisomy 7, 9 and 22.[5] Also duplication of SIX1, SIX6, and OTX2 was presented.[38] Some researchers suggest that the origin of this syndrome is due to the abnormal development of vascularization in 4th week of pregnancy when it comes to the development of the 1st and 2nd pharyngeal arches.[5] Moreover a lot of external factors like vasoactive medications, smoking, cocaine, exposure to thalidomide, hormonal therapy, drugs in the course of some diseases like antineoplastic medicament tamoxifen can contribute to

interference of normal growth of 1st and 2nd pharyngeal arches.[5,37,38] Studies have shown that infants of diabetic mothers are more prone to OAVS.[40,37,38] The increased risk of the syndrome is also closely related to maternal hypothyroidism, celiac disease, vaginal bleeding during pregnancy or premature birth,[18] One of the articles has shown lack of connection between occurrence of OAVS and parental age, length of menstrual cycle or previous cases of miscarriages.

However, statistically significant correlation was observed between pregnancy at an older age of both parents and more frequent births of children with GS.[18] Increasing risk was observed in case of multiple pregnancies especially in twins.[4,13,28,30] Moreover, two to three times more often structural defects affected monozygotic twins.[39] Some of the researches refer to higher occurrence of OAVS in pregnant with *in vitro* fertilization.[37,39]

Prenatal diagnostics

There are no specific genetic tests for the diagnosis of GS although various locus of chromosome abnormalities have been identified. In families with children presenting GS phenotype, it is important to examine their parents and siblings to identify all clinical manifestations of OAVS to assess the risk of recurrence of this defect in the future. Also three generation family profile should be prepared to identify all abnormal characteristic and GS-genetic counselling is advised if any relative with such problem is present.[51]

Non-invasive prenatal diagnostics (fetal diagnostics) is advised in all cases of previously recognized GS in the family. Fetal ultrasound allows to detect microtia, preauricular tags and/or asymmetric mandibular hypoplasia in severe defects, and 3D detailed scans can enable to identify milder cases as well. Invasive diagnostics (the puncture of trophoblast or amniocentesis) can be considered only in cases when genetic mutation causing GS is confirmed in fetus.[43,44]

Treatment: Treatment of patients with GS is complex and should be planned according to patient's age, extent and severity of observed abnormalities. Hence the treatment necessitates an individualized multistage and multidisciplinary approach. The therapy usually begins early and takes a longer course. We discuss a general scheme of treatment strategy in patients with GS, which should be modified as per the clinical manifestation. Over the years, the new symptoms can be observed in new parts of the body and previously diagnosed abnormalities become more pronounced.[38]

Treatment in newborns and children: In the diagnosis of GS, extremely important step is the examination of newborns, to ascertain the congenital malformations requiring prompt and timely correction by seeking appropriate specialized consultations. Neonatologists and Paediatricians play a paramount role in the early diagnosis soon after the birth. The most common symptoms occurring in these patients are tachypnea, stridor, cyanosis, retractions, and episodic upper airway obstruction with apnoea.[44-46] Problems with airway management.

Appear in infants and worsen with adolescence.[47,48] Decrease of the oropharyngeal airway can be caused mainly attributed to the deformation in craniofacial area like: retruded maxilla and mandible, midface and mandibular hypoplasia.

In patients with GS, aberrant configuration of the nasopharynx involving pterygoid processes, and adenoids, narrowing of the antero posterior and lateral dimension of the airway at the level of the larynx may be also observed.[21,40,41] As a consequence of which patients may suffer from asthma, recurrent pneumonias, bronchitis with pulmonary aplasia of a left upper lobe. All disturbances in the airways and facial deformities may result in difficult intubation, airway compromise, increased work of breathing, severe obstructive sleep apnoea, and even lead to respiratory distress. Nasal airway obstructions can be reduced by turbinectomies or septoplasties to establish a good functional nasal airway as early as six months of age. Other methods of treatment include procedures like tonsillectomy adenoidectomy and uvulopalatopharyngoplasty.[2]

It should be considered that in this syndrome some life threatening cardiovascular defects may appear, in which cardiovascular collapse is likely to occur and such conditions require immediate intervention after birth such as: transposition of the great vessels and aortic arch anomalies. In patients with large defects, the defect closure is performed electively in infancy or childhood. Some septal defects may close spontaneously, depending on their size and location In neonates suspected to have congenital heart disease prompt diagnostics should be performed after running tests like chest X ray ,echocardiography, coronary angiography and invasive cardiac catheterization.

Maxillofacial treatment intervention: In GS, craniofacial deformities with different severity are observed like cleft face, cleft lip, cleft palate, velopharyngeal inadequacy and hemifacial microsomia, and thus all newborns should be examined by maxillo-facial and plastic surgeon for the establishment of long-lasting, multi-stage treatment plan. Surgical

correction of these defects will improve feeding and swallowing in neonates and infants. Hypernasal speech in older children may require a pharyngeal flap to improve speech quality. For aesthetic reasons preauricular appendages can be removed in the first year of life. Patients with transverse facial clefts, cleft lip and palate need more complex surgical care. A special additional patient's schedule is created as these children usually undergo several surgery procedures in proper age, e.g., cleft lip repair is performed at the age of 3 months,

Repair of soft and hard palate at nine months to one year, maxillary bone grafting at the age of 9-11 years.[2]

The time of surgical correction of maxillo-facial deformities should depend on the severity of observed defects, chosen treatment method and patient's needs and expectations. For unification of heterogeneous presentation of unilateral craniofacial microsomia and better treatment planning different classification systems of mandibular hypoplasia have been proposed.[56,58] However, the most commonly used is Pruzansky-Kaban system (Table 2).[56,59]

Table 2: The Pruzansky-Kaban classification system.[46,49]

Type I	Small mandible with normal morphology
Type IIa	Abnormal size and shape of mandibular ramus
Type IIb	Abnormal size morphology and location of mandibular ramus and TMJ
Type III	Lack of mandibular ramus, condyle and TMJ

Surgical treatment includes costochondral and bone grafts, classic osteotomies (Obwegeser-Dal Pont's mandibular osteotomy, Le Fort I/II/III level osteotomy, genioplasty), distraction osteogenesis alone and in combination with grafts and patient-fitted total temporomandibular joint (TMJ) prostheses.[16,38,60] Total joint prostheses are advocated especially in non growing patients, although in severe cases they may be indicated earlier during growth, because they are very predictable relative to positioning of mandible. This therapeutic concept can be combined with contralateral mandibular ramus sagittal split osteotomy and maxillary osteotomies performed during one operation with counter clockwise rotation of the maxilla mandibular structures.

Malocclusion is very common among children with GS and requires consultation. Moreover, different spectrum of tooth discrepancies can be observed from agenesis of third molars and second premolars, enamel and dentin deformation, delay in tooth development to

supernumerary teeth. Correction of the occlusion determines improvement in speaking, chewing, swallowing and also positively affects the appearance of the patient. Orthodontic therapy begins in children with removable (functional) orthodontic appliances. It is then continued with fixed orthodontic appliances in children with secondary dentition. Orthodontic treatment is also extremely important as a part of preparation for surgical correction of the facial deformities.[11,14]

Ophthalmological consultation

Very often surgical treatment is needed in case of epibular dermoids, dermoid cyst on cornea and/ or sclera, and coloboma. Children with such defects, who require operation, are treated surgically at different ages, usually within first 2-3 years of their life. Epibulbar dermoids are solid, white-yellow or pinkish benign tumors (episcleral choristomas). They are built with cutaneous and subcutaneous tissue and sometimes they contain hair and other skin structures. They are classified into three grades according to their size. Most of patients with epibulbar dermoids have no symptoms. In some cases, local irritation can be caused by hairs or other dermal structures Surgical treatment is primarily used to limit cosmetic defect. For larger defects except for simple keratectomy also amniotic membrane transplantation, autologous limbal stem cell allograft or pericardial patch graft is needed. Only small asymptomatic grade I limbal dermoids should not be treated surgically because such treatment may lead to development of pseudopterygium.[61] Other ophthalmological anomalies that can be observed in these patients are coloboma, nystagmus, microphthalmia, anisocoria, aplasia of trigeminal nerve and strabismus.[3,61] It should be mentioned that ocular abnormalities in GS predispose to amblyopia development as a result of anisometropia, high degrees of refractive defects, strabismus, deprivation of vision may be caused by vision obstructing disorders.

Orthopedic consultation

In GS, structural disorders of the vertebrae (mostly in the cervical part of vertebral column) are commonly observed. Frequent abnormalities in vertebrae result in functional impairment, e.g., scoliosis. Most frequent is torticollis which results in restricted mobility of the neck. Cervico-thoracic scoliosis, thoraco-lumbar scoliosis and kyphosis are also observed. It is of a great importance to recognize skeletal abnormalities and to implement a proper treatment and rehabilitation as soon as possible and to assure an adequate development.[12]

Very few patients with GS also reported abnormalities of the urogenital system, dysfunction of VII cranial nerve may be a consequence of not only impaired facial muscles function but

also of conduction deafness (dysfunction of the temporal and zygomatic ramus of facial nerve).[14] The dysfunction of VII nerve can result from its abnormal course and unilateral aplasia of the trigeminal nuclei. The GS can also manifest itself through intellectual disability and cognitive impairment. Psychiatric, psychological and pedagogical consultation will let them adapt to the school program.

CONCLUSION

Patients with GS present with wide range of abnormalities and variations in the severity of symptoms posing a challenge for clinicians. All of this necessitates a customised approach to each patient with involvement a team of specialists in establishing final diagnosis and appropriate treatment planning. It is a complex, long-lasting, multidisciplinary process and should be divided into multiple stages, according to patient's age, as well as the extent and severity of observed abnormalities.

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