Goldenhar syndrome: current perspectives

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Background: **Progress in medical branches that has taken place since the first child with Goldenhare syndrome (GS) had been described in 1952 by Maurice Goldenhar, facilitated better understanding of this congenital defect. It also gave new perspectives and the opportunity to achieve satisfactory treatment results, mainly due to development of surgical techniques.**

Data sources: **Based on the literature and own experience, we discussed the phenotype of presentation of GS, ethiopathogenesis, genetic counselling and treatment with particular emphasis on surgery correction of hemifacial microsomia.**

Results: **The spectrum of GS abnormalities ranges from mild to severe ones and include patients with barely noticeable facial asymmetry to very pronounced facial defect with more or less severe abnormalities of internal organs and/or skeleton. It is characterized most commonly by impaired development of eyes, ears, lips, tongue, palate, mandible, maxilla, zygomatic and orbital structures and deformations of the teeth structures. Ethiopathogenesis is multifactorial and dependent on genetic and environmental factors but there are still many unknowns about the syndrome which should be revealed.**

Conclusions: **Patients with GS due to a large variety of abnormalities and different severity of symptoms pose a challenge for clinicians. All of this necessitate an individual approach to each single patient and involvement a team of specialists in treatment planning. It is a complex, long-lasting, multidisciplinary process and should be divided into stages, according to patient's age, as well as the extent and severity of observed abnormalities. Neonatologists and pediatricians are involved in care of these patients from the onset.**

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Review article

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] 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 derive 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.[2-4] According to some authors for this reason other name like hemifacial microsomia shouldn't be used interchangeably while referring to this syndrome.[5,6] Various studies have shown that this defect occur from 1:3500 or 1:5600 to 1:45 000 live births.[7,8]

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) 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 and are presented in Table 1. The most common symptoms of GS are epibulbar dermoids, dacryocystitis, auricular abnormalities, preauricular appendages, preauricular fistulas and hypoplasia of the malar bones, mandible, maxilla and zygomatic arch (Figs. 1 and 2).[18] Moreover, in children with GS can also be observed: 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.[19-21]

Table 1. Abnormalities in Goldenhar syndrome

Ocular symptoms[2-4,9-13]	
Epibular dermoids	Cleft eyelid
Microphtalmia	Exophthalmia
Anophtalmia	Strabismus
Eyes asymmetry/dysmorphy	Lipodermoids
Coloboma	Lacrimal duct artresia/stenosis
Auricular symptomps[2-4,9-11]	
Dacryocistitis	Atresia of the external auditory canal
Preauricular appendages	Ear dysplasia with or without hearing loss
Preauricular fistulas	Middle and inner ear abnormalities
Anotia	Ears asymmetry
Microtia	
Cranio-facial deformities[2-4,9-13]	
Abnormalities of the 1st and 2nd pharyngeal arches	Bifid tongue
Facial asymmetry	Hypoplasia of the (facial skeleton) mandible and/or maxilla
Hemifacial microsomia	Malocclusion
Cleft face	Tooth discrepancies
Cleft lip	Agenesis of 2nd premolars and 3th molars
Cleft palate	Supernumerary teeth
Macrostomia	Malformations of enamel and dentin
	Delay in tooth development
Skeletal abnormalities[2-4,9-14]	
Cleft spine	Extremities anomalies
Microcephaly	Club foot
Dolichocephaly	Radial hemimelia
Plagiocephaly	Thumb abnormalities
Vertebral defects	
Internal organs abnormalities	
Heart[3,15]	
Atrial and ventricular septal defects (the most frequent)	Fallot tetralogy
Conotruncal defects	Persistent truncus arteriosus
Aortic arch anomalies, Transposition of the great vessels	Other outflow tract abnormalities Dextrocardia
Urogenital anomalies[3,16]	
Ectopic kidneys	Renal agenesis
Fused kidneys	Multicystic kidneys
Double ureter	Hydroureter
Hydronephrosis	
Central nervous system[3,17]	
Diffuse cerebral hypoplasia	Hydrocephalus due to aqueduct of Sylvius stenosis
Dilated lateral cerebral ventricles or asymptomatic hydrocephalus	Corpus callosum lipoma
Asymmetric lateral ventricles	Absence of septum pellucidum
Corpus callosum dysgenesis	Diffuse cerebral hypodensity
Frontal hypodensities	Facial palsy
Microcephaly	Trigeminal anesthesia
Encephalocele	Developmental delay
Spine deformities	Holoprosencephaly
Arnold–Chiari malformation	Hypothalamic hamartoma
Aplasia/hypoplasia of temporomandibular joints	
Gastrointestinal tract[3]	
Rectal atresia	Trachea-esophageal fistula
Aeosophagal atresia	
Respiratory system[3]	
Abnormal anatomy of larynx and pharynx	Disorder of lobular anatomy of lungs

Airway obstruction and sleep apnea symptoms can be life-threatening problems related to the retruded maxilla and mandible constricting the oropharyngeal airway as well as associated nasal airway obstruction.

Due to the different scope of clinical phenotype, there are still no established guidelines for the minimum diagnostic criteria for GS. Some authors emphasize that presence of isolated hemifacial microsomia together with a family history of this syndrome should be considered to be diagnostic.[3]

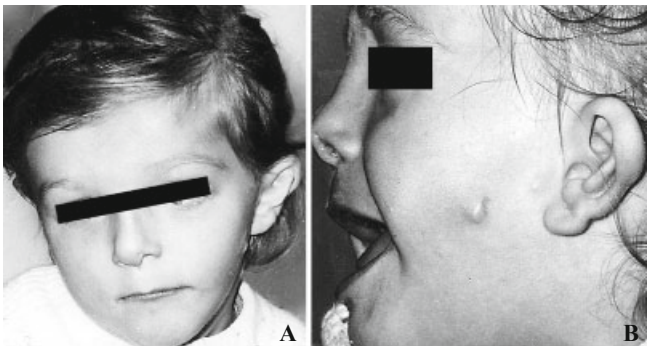

Fig. 1. A: Hemifacial macrosomia, epibulbar dermoids; **B:** Preauricular appendages and earlobe dysplasia in a child with goldenhar syndrome.

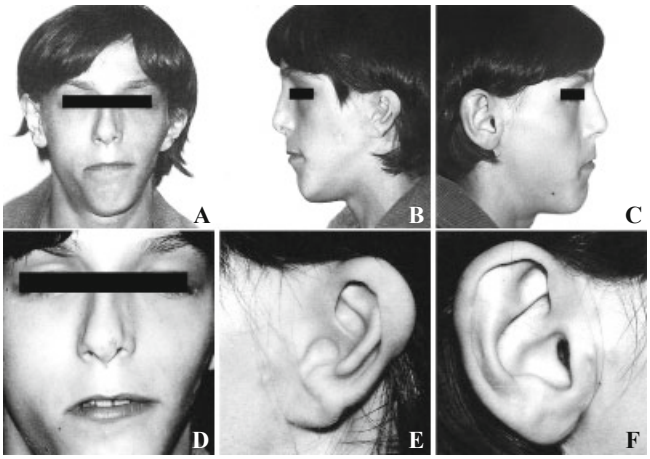

Fig. 2. A: Child, age 14, with Goldenhar syndrome manifestation, facial asymmetry caused by bilateral maxillary hypoplasia, more pronounced on the left side, leftsided zygomatic bone and mandible hypoplasia; **B:** Right side of this patient; **C:** Left side; **D:** Deformation of left nostril; **E:** Left ear located lower than the right one, on the left side-preauricular appendages, hypoplasia and improper shape of left auricle; deformation of the wing of the left nostril and nasal septum; **F:** Right earlobe.

Etiopathogenesis of Goldenhar syndrome

Etiopathogenesis of GS is still very poorly known and in lot of cases unexplained. However, genetic researches, nowadays conducted more frequently, let us know more and more about this congenital disease. We can suspect that 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 or recessive inheritance.[12,14,22-25] According to Beleza-Meireles et al,[3,12] there are authors who estimate 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 (as between siblings or from parents to children) were most often affected. And the risk of recurrence of this syndrome probably equals 2%-3%.[3] Nevertheless, most of the described cases of this syndrome appear sporadically.[3,23,26]

It is also noticeable that OAVS affects more male than female infants.[12,14,27] 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.[3] Also duplication of SIX1, SIX6, and OTX2 was presented.[28]

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 responsible for growth of craniofacial structures.[3] 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.[3,27,29]

Studies have shown that infants of diabetic mothers are more prone to OAVS.[27,30,31] The increased risk of the syndrome is also closely related to maternal hypothyroidism, celiac disease, vaginal bleeding during pregnancy or premature birth.[17] 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.[29]

Increasing risk was observed in case of multiple pregnancies especially in twins.[3,12,27,29] Moreover, two to three times more often structural defects affected monozygotic twins.[29] Some of the researches refer to higher occurrence of OAVS in pregnant with *in vitro* fertilization.[27,29]

Genetic counselling

There are no specific genetic tests for GS diagnosis although many chromosome abnormalities have been identified. This fact together with lack of the defined minimum clinical diagnostic criteria for GS cause difficulties in genetic counselling. Nevertheless, the genetic counselling is recommended for any individual who has an inherited or *de novo* chromosome abnormality. It must be noted that the prediction of all congenital malformations in another child with the same chromosomal disorder cannot be accurately done. In families with children presenting GS phenotype it is important to observe their parents and siblings to identify all clinical manifestations of OAVS (together with subtle ones)-it is important for assessment the risk of recurrence this defect in the future. Also three-generation family profile should be prepared to identify all abnormalities characteristic for GS-genetic counselling is advised if any relative with such problems will be found.[3]

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.[32,33]

Treatment

Treatment of patients with GS is complex and should be divided into stages, according to patient's age, as well as the extent and severity of observed abnormalities. The fact that the spectrum of phenotypic features is variable, the treatment necessitates an individual multistage and multidisciplinary approach. The therapy usually begins early and is long-lasting. Below we present a general scheme of treatment strategy in patients with GS, which should be individually modified. Over the years, the new symptoms can be observed in new parts of the body and previously diagnosed abnormalities become more pronounced which is due to growth retardation.[28] Consultation sections and information in Table 1 give the full picture of clinical manifestation of patients with GS.

Treatment in newborns and children

In the diagnosis of GS, extremely important is the first examination of newborns, when congenital malformations requiring prompt correction should be recognized. Within a few days of life other components of this syndrome are observed, requiring specialized consultations.

General pediatric care

Neonatologists and pediatricians are involved in treatment of patients with GS from the onset. Neonatologist is present at birth. He is also the one, who confirms the diagnosis of a congenital defect and take care of a newborn from the first day of its life. It is crucial to exclude life threatening conditions resulting from airway obstruction and

internal organ abnormalities. Treatment starts from the most important things that give the chance a newborn to survive and ends with operations from different surgery fields. Neonatologists and pediatricians are intend to identify problems that require referrals to other specialists. They are responsible for monitoring weight, height and development of children with GS. Anomalies in these parameters, if present, should be examined by the specialist (endocrinologist, gastroenterologist) who exclude, other than GS, possible causes. These patients require periodical further control examinations and checkup visits. The final success depends on close cooperation between pediatricians and other specialists involved in treatment.

Airway

Patients with hemifacial microsomia and GS commonly have severely decreased oropharyngeal airway as well as nasal airway obstruction. The most common symptoms occurring in these patients are tachypnea, stridor, cyanosis, retractions, and episodic upper airway obstruction with apnea.[34-36]

Problems with airway management appear in infants and worsen with adolescence.[37,38]

Decrease of the oropharyngeal airway can be caused mainly by deformation in craniofacial area like: retruded maxilla and mandible, midface and mandibular hypoplasia.[39]

In patients with GS, aberrant configuration of the nasopharynx involving pterygoid processes and adenoids, vascular ring caused by right-sided aortic arch, narrowing of the anteroposterior dimension of the airway at the level of the larynx or narrowing in the lateral dimension at the same level are also observed.[21,40,41] As a consequence, patients with this syndrome may suffer from asthma, recurrent pneumonias, bronchitis or are diagnosed with pulmonary aplasia of a left upper lobe.[21]

All disturbances in the airways and facial deformities may result in: difficult intubation, airway compromise, increased work of breathing, severe obstructive sleep apnea, and even lead to respiratory distress. Such problems can increase mortality and morbidity among this group of patients and, as a result, tracheostomy is still the standard procedure for airway control.[36,38] Research showed that 22% of more severe cases may require a tracheostomy at birth and the patients with ventriculoperitoneal shunt have undergone this procedure more frequently.[42]

The retruded maxilla and mandible depending on the severity will decrease the oropharyngeal airway. Sometimes the early management of children with this problem is indicated to advance the mandible to open up the oropharyngeal airway. Nasal airway obstruction is common in these patients and may require reduction turbinectomies or septoplasties to establish a good functional nasal airway. Other methods of treatment include procedures like: tonsillectomy and adenoidectomy, uvulopalatopharyngoplasty, anterior tongue reduction, and endoscopic tracheal granuloma excision. Most of these airway interventions are performed within the first 6 months of life.[39]

Researches have also shown that frequent treatment of obstructive sleep apnea is nasal continuous positive airway pressure ventilation applied with a mask through the nares, or if it isn't effective-nasopharyngeal tube, which is also used in case of upper airway obstruction.[34,43]

After a diagnosis of congenital disease, to prevent later complications, it should be remembered to evaluate patients for signs of upper airway obstruction such as tachypnea, stridor, sleep apnea and hypercapnia which can be significant in the later treatment.[34,44]

Cardiology consultation

It is performed in children with craniofacial defects within first days of life to search for congenital heart defects and malformations of major blood vessels. 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 treatment after birth such as: transposition of the great vessels and aortic arch anomalies (coarctation of the aorta and aortic stenosis). Other disorders observed in children with GS are clinically significant but do not require prompt interventions or they are clinically insignificant and do not require cardiac surgery (dextrocardia). Infants with atrial and ventricular defects with severe symptoms may require operation treatment within the first few months. 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. Despite the efforts to detect critical congenital heart defects in the fetal life or immediately after birth, large population of neonates with heart anomalies are undiagnosed until after developing serious symptoms.[45]

In neonates suspected to have congenital heart disease prompt diagnostics should be performed. Chest X ray is done to assess pulmonary vascular marking and cardiomegaly and to rule out pulmonary diseases. Also electrocardiography is often done for detecting some defects aberrations in electrical axis (left axis deviation or right axis deviation) together with clinical examination may suggest a proper diagnosis. The most valuable tool for diagnosing heart defects is echocardiography-the heart anatomy can be easily assessed, as well as systolic ventricular function, chamber dimensions, wall thickness and with the

use of Doppler technique-the pressure gradients or regurgitation flow through valves. Invasive diagnostics like cardiac catheterization is rarely applied in some cases coronary anatomy is assessed in angiography prior to arterial switch operation in transposition of great arteries.[45]

Surgery consultation

In most cases, the abnormalities of digestive duct manifest within the first hours of neonate life and require prompt surgical 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 years 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 9 months to 1 year, maxillary bone grafting at the age of 9-11 years.

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.[46-48] However, the most commonly used is Pruzansky-Kaban system (Table 2).[46,49] 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) prosteheses.[13,28,50-54] 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 counterclockwise rotation of the maxillomandibular complex.[13,52] All these techniques possess advantages and disadvantages (Table 3). It should be emphasized that

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

TMJ: temporomandibular joint.

Table 3. Different surgical techniques in maxillo-facial defect treatment

Treatment methods	Advantages/characteristics	Limitations/complications
Grafts: Costochondral graft Autogenous bone from the iliac crest Rib graft Temporal skull region Outer cortex of the unaffected side of the mandible	They are used to lengthen the mandible[47,51,55-57] There is a possibility to reconstruct the TMJ and mandibular ramus[47,55,58-61]	Facial asymmetry-unpredictable growth and different growth pattern of healthy and hypoplastic side, overgrowth of the graft, overgrowth of normal (not affected side), bone resorption[57,60,62,63] 3D overgrowth of the graft diminishing the range of mandibular movements[11] Risk of graft rejection and/or infection[11,57]
Classic osteotomies	They are especially useful for correction of secondary deformity[53]	It can't be performed in growing patients These are large surgical procedures with different complications impaired healing, malocclusions, sensory disturbances Elongation and rotation of mandibular ramus fails in severe deformities[53]
Distraction osteogenesis	Effective technique in young patients[64-66] Used to lengthen the jaw and mandible ramus	Not suitable for TMJ reconstruction High risk of mild infection during active and passive period of lengthening[11,57] Relapse of the distracted bone occurs very often[67]
Distraction osteogenesis with bone grafts	This method combines the advantages of grafts and distraction osteogenesis The good choice for severely affected patients[54]	This method combines the disadvantages of grafts an distraction osteogenesis[54]
Total temporomandibular joint prosthesis	Can be used for correction of major deformities Individually patient-fitted titanium prosthesis Osseointegration of the fossa and ramus component is present Gives the predictable outcomes Prosthesis works in poorly vascularized recipient site Single-stage orthognathic surgery can be performed[13,52]	Requires virtual, time consuming planning or preparation of stereolithic model Has no potential growth Possible allergic reactions Requires time to manufacture the prosthesis (6-8 wk) [13,52]

TMJ: temporomandibular joint.

classic osteotomies can be performed only in patients after the end of the osseous growth.

Goldenhar syndrome is believed to have a progressive nature and though early correction of observed abnormalities as well as reduction of secondary deformity is needed.[68-70] Some authors advocate delayed surgical intervention (until bone growth is ended) to perform single stage final correction of the defect.[71,72] Such strategy can be applied in mild syndromes. Nevertheless, in patients with severe facial defects early correction with multi-stage reconstruction seems to be a method of choice, to prevent a negative psychosocial effects.[73]

Orthodontic consultation

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]

Otolaryngological consultation

This is a very important part of diagnostics of patients with GS, because this syndrome is frequently accompanied with hearing loss. Laryngological examination should be performed with thorough otoscopic and hearing assessment. Diagnosis and treatment of hearing loss (hearing prosthetics, cochlear implants) should be performed as soon as possible to ensure the proper speech development. Furthermore, it is important to assess the construction of the pharynx and larynx. Abnormalities of these organs can cause speech disorders, problems with breathing and sleeping apnea.

Ophthalmological consultation

This is also a crucial element of diagnosis of children with GS. 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.[74] Dermoid cyst can consist of skin, hair, sweat glands, pocket of blood, fat, bone, etc. In young children, they often appear on the eyebrow, but also on cornea and/or sclera. Dermoid cyst may exist without any symptoms (except cosmetic inconvenience). They can be surgically removed preferably in one piece, and any spillage of cyst content should be avoided.[75]

Coloboma is a congenital defect of the structures of the eye (iris, retina, choroid and optic disc). It is a consequence of absence of normal tissue in above mentioned structures and results in their abnormal shape. People with coloboma may have no symptoms, light sensitivity, photophobia or they may have mild to severe vision impairment, depending on the location and size of the coloboma. Large colobomas may even cause vision loss. Patients without vision impairment do not require surgery treatment. For better cosmetic effect patients with coloboma can use cosmetic contact lenses to make the pupil look round.[76,77]

Other ophthalmological anomalies that can be observed in these patients are nystagmus, microphthalmia, anisocoria, and strabismus.[1,78] 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 caused by vision-obstructing disorders.[1,78]

Also a first manifestation of aplasia of trigeminal nerve can be of the form of ophthalmological symptom-neurotropic keratopathy.[79] The assumption of presence of such anomaly may bring anaesthesia of the cornea of the affected side. Hypoplasia or aplasia of trigeminal nerve is confirmed in radiological imaging-magnetic resonance imaging.[80] Patients with GS may develop a severe type of keratopathy with extensive ulceration. In such cases the most extended surgical methods are the best treatment option-multilaminar amniotic membrane transplant, which supply the basal membrane with epithelial cells.[81-83] Early diagnosis of corneal hypoesthesia or anaesthesia may prevent the occurrence of ocular complications and also contribute to proper visual development.[79]

Orthopedic consultation

Locomotor system is very important for proper

psychomotor development. In children with GS this process may be impaired by the occurring skeletal deformations. Orthopedic consultation with accurate radiological examination is necessary to identify indications for conservative or surgical treatment. It consists of classic radiographs and computed tomography, which is preferred in diagnosing spine pathology.[84]

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.[84]

Rib anomalies and deformities in the cervical and thoracic spine have equal frequency. Anomalies in lumbar spine are less often.[85]

Depending on the severity of the defect we should consider different methods of treatment: surgical or non-surgical. Non-surgical approach includes bracing and physical therapy. We should remember that early started treatment can prevent severe curvatures.[34] Similarly, in case of congenital scoliosis, we achieved the best results when treatment is initiated before child completes three years of life. The choice of surgical treatment depends on such factors like patients age, type of anomaly, the degree of deformation.[86] The best time for surgery treatment is 2-3 years of age.[87] Surgical procedures include *in situ* fusion, convex epiphysiodesis, hemivertebral excision, single/double stage correction with instrumentation and fusion, reconstructive osteotomy, vertebral column resection or growing rods.[88]

Congenital scoliosis can develop slowly so all patients necessary need radiological assessment at four to six months periods.[88] In some cases, extremity anomalies can be seen such as club foot, radial hemimelia, and thumb abnormalities. Clubfoot can be treated by rehabilitation through exercise and a plaster or orthopedic splint. Later also stabilizing rails and orthopedic footwear can be used or Ponseti method using semirigid synthetic soft cast. Sometimes children under 2 years may require surgical treatment.[89]

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.

Nephrology consultation

It should be remembered that children with GS may have congenital defects of urogenital system. Careful diagnosis should be taken and further treatment depends on the results of examination. For the screening purposes, an ultrasound examination should be performed in any child with GS. Very often these defects are underdiagnosed.

Neurological consultation

The most common reason for consultation with a neurologist is feeding problem in children. They are caused by neurological disorders such as abnormal muscle structure (asymmetric development of masticatory muscles), agenesis of salivary glands and salivary fistulas and improper nerve supply in the face region (especially in oral cavity and palate).[90,91] In patients with cleft palate a special bottle like Haberman bottle should be used. In severe cases it is necessary to use nasogastric feeds or perform a gastrostomy to provide a proper nutrition. 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).[11] The dysfunction of VII nerve can result from its abnormal course and unilateral aplasia of the trigeminal nuclei. In people with GS also the function of other cranial nerves may be impaired. In case of microphthalmia, abnormal structure of the skull and neurological disorders (such as epilepsy, abnormal muscle tension, abnormal reflexes) it is recommended to use neuroimaging (magnetic resonance imaging for central nervous system defects diagnosis). Such diagnostics can confirm or exclude different brain anomalies that can be hydrocephalus, occipital and frontal encephaloceles, unilateral arhinecephaly, lipoma of corpus callosum, dermoid cyst, teratoma, Arnold-Chiari malformation, lissencephaly, arachnoid cyst, holoprosencephaly, porencephalic cyst and hypoplasia of the corpus callosum.[78,92,93] Obviously, patients with epilepsy require adequate medical pharmacological treatment.

It should be mentioned that children with GS are at increased risk of developing mental retardation with different, multiple, sometimes severe manifestations.

Psychiatric consultation

The GS can also manifest itself through intellectual disability and cognitive impairment. Psychiatric, psychological and pedagogical consultation will let to adapt the school program to an individual patient. Patients' physical appearance and lack of its acceptance can lead to psychiatric disorders and may require psychiatric consultation and therapy. Moreover, disease of a child affects the functioning of a whole family, changing parents behavior and relations with other people. The stress of having a deformed child can have a profound effect on the parents that could lead

to divorce and counseling/therapy may be necessary. The parents of a child with congenital defects often experience various strong emotions including anxiety, feelings of powerlessness and helplessness, grief, anger, rebellion and even remorse.[94] Constant tension and nervousness may lead to various conflicts. On the other hand, this situation is also reflected in relations with a child who is experiencing a lack of emotional support.

The aim of psychiatric consultation is to assess the potential psychological problems and diagnose mental disorders. Psychiatrics often refer children and parents to psychotherapist. In some cases of severe personality disorders additionally psychiatric medications are prescribed.[95]

In children with GS, alarming symptoms that suggest autism may be observed like: 1) infant does not babble by 12 months; 2) infant does not use gestures by 12 months; 3) child is not able to speak a word by 16 months; 4) child cannot build spontaneous two-word phrases by 24 months; 5) communication problems or social skills deficits, at any age.[96]

Failure to meet any of the following milestones should bother and require prompt psychiatric consultation. In the early childhood, typically in the first 2-3 years of the child's life different signs of autism may be present.[97] They often develop gradually. In some children at the beginning the mental and psychological development is not disrupted and then they regress.[98] Different autism-specific screening tools are available that should be performed in every child who present alarming symptoms. The most popular are the *Modified Checklist for Autism in Toddlers*, the *Early Screening of Autistic Traits Questionnaire*, and the *First Year Inventory*, the *Checklist for Autism in Toddlers*.[99]

The diagnosis of autism is based on child behavior.[100] Several diagnostic instruments are available. Two diagnostic tests are commonly used. One is the *Autism Diagnostic Interview-Revised* which is based on parent interview. The second one is the *Autism Diagnostic Observation Schedule* that relies on observation and interaction with the child.[101]

Management of children with autism comprises of lessening associated deficits and family distress, increasing quality of life and functional independence of affected children and adults. To achieve these goals many therapeutic options are available like different psychosocial interventions, intensive, sustained special education programs and behavior therapy, and medications.[99,102,103] These interventions start early, after recognition of behavioral problems. Developmental models, social skills, speech and language therapy as well as structured teaching, applied behavior analysis and occupational therapy are the therapeutic options.[97] Psychoactive or anticonvulsants drugs (antidepressants, stimulants, and antipsychotics) are prescribed when behavioral treatment fails or in children with severe symptoms.[104-106]

Treatment in adults

It is usually a continuation of treatment initiated in childhood. It includes reinterventions and corrections of secondary deformities. Operational procedures in nongrowing patients give a more predictable effects and they are more streamlined as the bone growth is ended. Facial asymmetry can be diminished with classic osteotomies and genioplasty. For patients who had TMJ reconstruction with grafts and who require reintervention a total TMJ prosthesis combined with orthognathic surgery should be recommended.

Patients with GS should undergo orthodontic treatment in adulthood as a continuation of that started in childhood. Orthodontic treatment in adults may consist of maintaining proper occlusion by retentive treatment or include secondary correction of malocclusion. These goals are achieved with fixed orthodontic appliances.

Also mental disorders require long-lasting treatment, which starts in childhood and continues in adulthood.

Conclusions

Goldenhar syndrome is a rare congenital defect. The spectrum of observed symptoms and their severity differs among affected patients. Treatment of people with GS is a complex process and depends on the clinical manifestation and patient's age. In some newborns, due to life threatening internal organ abnormalities or airway obstruction a prompt surgical intervention is needed within the first few hours after birth.

Correction of all malformations requires long-lasting, multistage and complex treatment plan. Operation of facial defects is a challenge because in some children except for hemifacial microsomia also TMJ aplasia/hypoplasia and orofacial clefts are being observed. In such children long-term outcomes of treatment are hard to foresee, not only because of complexity of the defect but also because of different patterns of bone growth in affected and non-affected side.

In some milder cases, a different surgical strategy can be applied, involving late corrective surgery when the bone growth is ended. This therapeutic option facilitate to perform more streamlined and more predictable treatment.

In conclusion, we believe that to achieve satisfactory treatment results involvement of a team of different

specialists is crucial. It is also essential to understand patient's and its family needs, meet their expectations, and establish viable and individual treatment plan. Proper interdisciplinary, well-thought-out treatment can lead to acceptable quality of life of patients with GS.

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