

## PEDIATRICS

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# RARE CARDIO-RESPIRATORY FINDINGS IN GOLDENHAR SYNDROME (case report)

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**Abstract:** The Goldenhar Syndrome is the rare congenital abnormalities that include Facio-Auriculo-Vertebral Spectrum, First and Second Branchial Arch Syndrome, Oculo-Auriculo-Vertebral Spectrum, oculo-auriculo-vertebral disorder. Oculo-auriculo-vertebral disorder (OAVD) represents the mildest form of the disorder, while Goldenhar syndrome presents frequently as the most severe form. Hemifacial microstomia appears to be an intermediate form. Goldenhar Syndrome includes patients with facial asymmetry to very severe facial defects (resulting from unilateral facial skeleton hypoplasia) with abnormalities of skeleton and/or internal organs. The most significant are epibulbar dermoids, dacryocystitis, auricular abnormalities, preauricular appendages, preauricular fistulas and hypoplasia of the malar bones, mandible, maxilla and zygomatic arch. Some patients are found to have oculo-auriculo-vertebral disorder, namely 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), psychosocial problems, autistic behaviors. The authors describe the clinical case of Goldenhar Syndrome in boy a 3-months-year-old. This case demonstrates a rarely described association of oculo-auriculo-vertebral disorders, malformation of respiratory system (hypoplasia of the lower lobe of the left lung with relaxation of the left cupula of the diaphragm), heart abnormality (atrium septal defect).

**KeyWords:** Goldenhar Syndrome, children, diagnostic



The multiple congenital malformations (MCM) are defined as a combination of anomalies in the development of two or more body systems. The frequency of diagnostic errors in the MCM structure is high both in Ukraine and Europe. Etiology of MCM is poorly understood, in view of the rare cases, as well as due to lack of specific laboratory verification of the diagnosis. According to the World Health Organization (WHO), about 7% of infant deaths worldwide are due to congenital pathology, 46% of them are children with congenital malformations who died under one year of age [1].

Goldenhar Syndrome (GS) - Q87.0 (Facio-Auriculo-Vertebral Spectrum (FAV), First and Second Branchial Arch Syndrome, Oculo-Auriculo-Vertebral Spectrum (OAVS), oculo-auriculo-vertebral disorder (OAVD)).

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Goldenhar Syndrome ranks second in incidence after cleft lip and palate [2, 3]. Oculo-auriculo-vertebral disorder (OAVD) represents the mildest form of the disorder, while Goldenhar syndrome presents frequently as the most severe form [4].

Hemifacial microstomia appears to be an intermediate form [4]. Goldenhar Syndrome includes patients with facial asymmetry to very severe facial defects (resulting from unilateral facial skeleton hypoplasia) with abnormalities of skeleton and/or internal organs [5]. The symptoms observed in this syndrome can be divided into groups according to the part of the body. The most significant are epibulbar dermoids, dacryocystitis, auricular abnormalities, preauricular appendages, preauricular fistulas and hypoplasia of the malar bones, mandible, maxilla and zygomatic arch [6]. Some patients are found to have oculo-auriculo-vertebral disorder, namely 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), psychosocial problems, autistic behaviors.

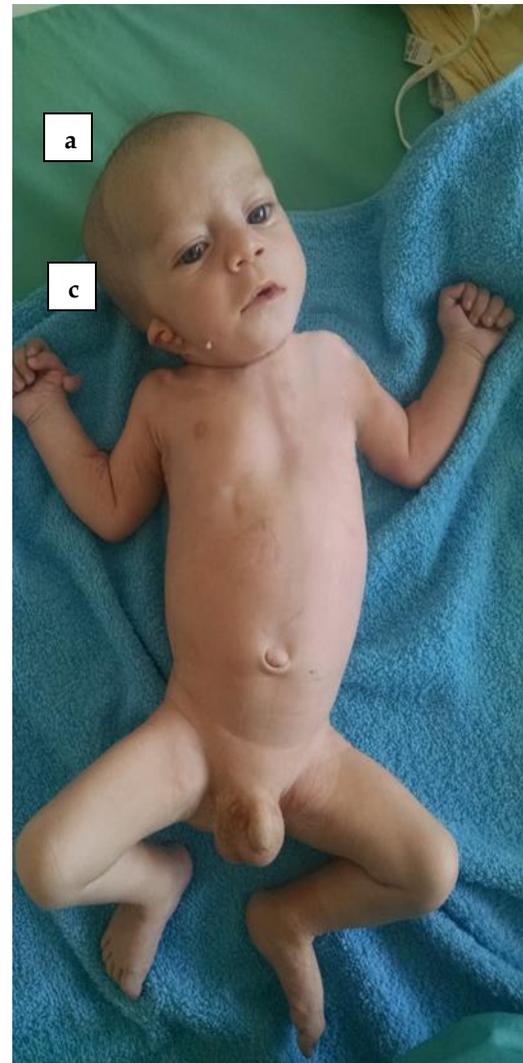
social problems, autistic behaviors [7-9]. Approximately 70% of cases are unilateral. In case of bilateral defects one side has the most severe malformations. The right side prevails over the left one with the incidence of 3:2 [5].

## CASE REPORT

The child was born from the pregnancy complicated by a respiratory viral infection in the gestation period of 4-5 weeks, suspected congenital heart disease according to the ultrasound data at 28 weeks, clinically and laboratory confirmed lues at 29 weeks. Full-term infant was born by caesarean section with Apgar score 5/7 and birth weight of 3.05 kg. There was no history of trauma to head and neck region or maternal teratogen agents. The child was also found to have bilateral asymmetry at birth. In the early neonatal period he suffered from respiratory failure which was managed by ventilation from the first day of life. Oxygen dependence was maintained up to 3 weeks of life. The child developed according to his age, without mental retardation or impairment of cognitive function.

On examination at 3 months he was found to have asymmetry of the face due to underdevelopment of soft tissues and bones of the facial skeleton on the right auricle: hemifacial (left side) microsomia, hypoplasia and deformation of the auricle, preauricular skin tags visualized from the earlobe (Figure 1), asymmetry of the eye fissures, gothic palate, predominance of the brain skull over the facial; short neck; long toes (Figure 1a); “hammer” deformation of the thumbs of both hands (Figure 1b); polydactyly of the right hand (Figure 1c), short tongue, thickening of the thumb on both hands, left-sided muscular torticollis, bilateral dropsy of testicles.

Body measurements: weight 3700 g, height 53 cm. The condition is severe, which is caused by ventilation disorders. The skin is pale and dry. It is noted that, with concern, marbling with an accent of the lower extremities. Turgor and elasticity of tissues are slow and reduced; subcutaneous fat is not sufficient. The head is hydrocephalic, evenly distributed. Muscular dystonia. The patient has previous history of cyanosis of the nasolabial triangle, dyspnea.



**Figure 1. A 3-months-old male patient:**  
1a - hemifacial (left sided) microsomia, hypoplasia and deformation of the auricle, preauricular skin tags visualized from the earlobe, asymmetry of the eye fissure;  
1b - “hammer” deformation of the thumbs of both hands;  
1c - polydactyly of the right hand.

**Diagnostic imaging findings:**

**Chest X-ray (Figure 2):**

- relaxation of the left side of the diaphragm, hypoplasia of the left lung?
- mild scoliosis
- Butterfly vertebrae (C5 and T1)



**Figure 2. A 3-months-old male patient. Chest's X-ray**

**ECG:** HR 125 min, sinus rhythm, electric axis deflected to the right side, right ventricular dilation and its systolic overload.

**Doppler echocardiography (body weight 3700 g):**

terminal diastolic diameter of the right ventricle - 14.6 mm (↑);

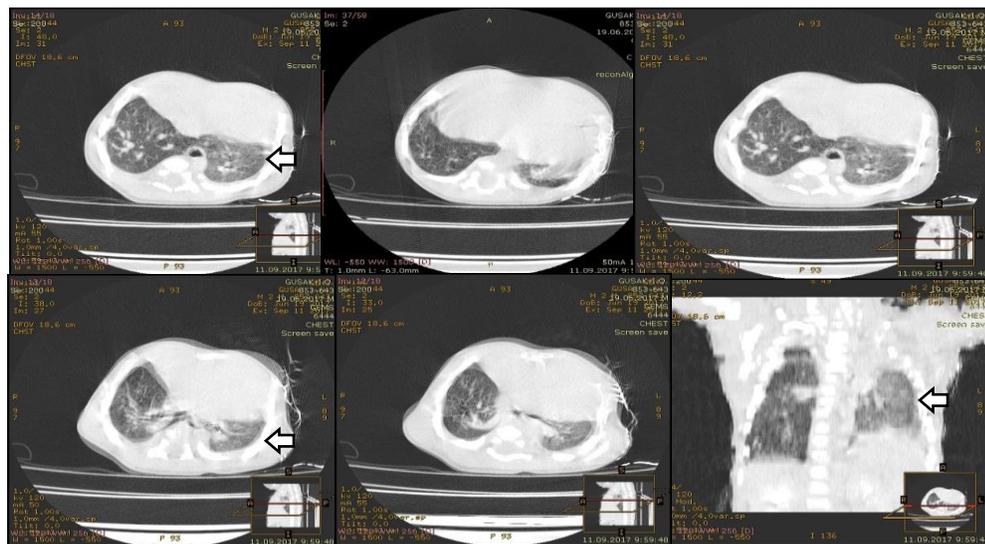
- diameter of the right atrium - 13.7 mm (↑);
- diameter of the pulmonary artery 12.7 mm (↑);
- mPAP, mean pulmonary artery pressure - 30 mm Hg (↑)

**Conclusion:** Dilation of the right atrium and ventricle, pulmonary arteria, left-right shunt in the central part of atrium septa, diameter = 4.6 mm. Turbulent flow in the pulmonary artery, pulmonary hypertension.

The patient was found to have developmental defect of the cardiovascular system in the form of a secondary defect of the atrial septum.

**High resolution computed tomography of chest organs (spiral pitch of 1 mm) with contrast (Tomoxol 300mg-9ml, IV) (Figure 3).**

- Poorly developed lung tissue of the left lung due to lower lobe hypoplasia with a small area of pulmonary tissue infiltration in the lower sections due to residual pneumonia.
- Trachea, main, lobar and segmental bronchi are freely passable throughout the whole length.
- Cupula of the diaphragm with a relaxed left contour.



**Figure 3. A 3-months-old male patient. High resolution computed tomography of chest organs (spiral pitch of 1 mm) with contrast: left lung lower lobe hypoplasia, cupula of the diaphragm with a relaxed left contour.**

**Conclusion:** Hypoplasia of the lower lobe of the left lung with relaxation of the left cupula of the diaphragm.

**The patient has a combination of rare findings that include:**

- hemifacial microsomia (right-sided),
- hypoplasia and deformation of the auricle (right-sided),
- polydactyly of the right hand (right-sided),
- preauricular skin tags (right-sided),
- “hammer” deformation of the thumbs of both hands,
- mild scoliosis,
- Butterfly vertebrae (C5 and T1) hypoplasia of the lower lobe of the left lung with relaxation of the left cupula of the diaphragm,
- Secondary atrial septum defect.

**Diagnosis: Goldenhar Syndrome:** oculo-auriculo-vertebral disorders, *Hypoplasia of the lower lobe of the left lung with relaxation of the left cupula of the diaphragm.*

#### DISCUSSION.

Goldenhar Syndrome (GS) has a sporadic cause. Some cases have family history. On the basis of these data, it can be assumed that the disease is more likely to have an autosomal dominant type of inheritance. Researchers suggest that GS may be caused by the interaction of many genes, possibly in combination with environmental factors (multifactorial inheritance). Some scientists think the syndrome reveals mutations of the GSC gene (14th chromosome). The GSC gene defines neural-crest cell-fate specification and contributes to dorsal-ventral patterning. Over activation in *Xenopus* promotes dorso-anterior migration and dorsalization of mesodermal tissue of the cells along with BMP-4 (Bone morphogenetic protein 4) [10-21].

The significant number of anomalies in the formation of musculoskeletal, nerve elements of the soft facial tissues that are presumably due to a vascular stroke in the region of the I and II gill slits of the embryos, coinciding with the replacement of the source of blood supply in the zone, which leads to pathological transformations of cell proliferation in the above-mentioned zone [22, 23].

Oculo-auriculo-vertebral spectrum represents three rare disorders that are apparent at birth (congenital), and are characterized by a wide spectrum of symptoms and

physical features that may vary greatly in range and severity from case to case. However, such abnormalities tend to involve the cheekbones, jaws, mouth, ears, eyes, and/or bones of the spinal column (vertebrae).

Abnormalities in Goldenhar syndrome [24-39]:

- ocular symptoms: epibular dermoids, cleft eyelid, microphthalmia, exophthalmia, anophthalmia, strabismus, eyes asymmetry/dysmorphism, lipodermoids, coloboma, lacrimal duct atresia/stenosis;
- auricular symptoms: dacryocystitis, atresia of the external auditory canal, preauricular appendages, ear dysplasia with or without hearing loss, middle and inner ear abnormalities, anotia ears asymmetry, microtia;
- cranio-facial deformities: abnormalities of the 1<sup>st</sup> and 2<sup>nd</sup> pharyngeal arches, facial asymmetry, hypoplasia of the facial skeleton, mandible and/or maxilla, hemifacial macrosomia, malocclusion, cleft face tooth discrepancies, cleft lip agenesis of the 2<sup>nd</sup> premolars and 3<sup>rd</sup> molars, cleft palate, supernumerary teeth, macrostomia, malformations of enamel and dentin delay in tooth development;
- skeletal abnormalities: cleft spine, abnormalities of extremities, microcephaly, club foot, dolichocephaly, radial hemimelia, plagiocephaly, thumb abnormalities, vertebral defects;
- internal organs abnormalities, heart: atrial and ventricular septal defects (the most common), Fallot tetralogy, conotruncal defects, persistent truncus arteriosus, aortic arch anomalies, transposition of the great vessels, dextrocardia;
- urogenital anomalies: ectopic kidneys, renal agenesis, fused kidneys, multicystic kidneys, double ureter hydroureter, hydronephrosis;
- central nervous system: 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, tri-

geminal anesthesia encephalocele, developmental delay, spine deformities, holoprosencephaly, arnold-chiari malformation, hypothalamic hamartoma, aplasia/hypoplasia of temporomandibular joints;

- gastrointestinal tract: rectal atresia trachea-esophageal fistula, esophageal atresia;
- respiratory system: abnormal anatomy of larynx and pharynx, disorder of lobular anatomy of lungs.

There are several classifications that reflect the degree of its severity. The most complete is OMENS [1]. It identifies three stages of the severity of the lesion of each of the malformation objects in hemifacial microsomia: the eye (orbit), mandible, ear, facial nerve and skeletal bones. Since defects are multiple and each structure is usually affected in different degrees, it looks like this: O2M3E3N2S1 \*. The asterisk reflects the presence of additional defects of non-skeletal-facial objects.

Symptoms of the following disorders may be similar to those of Goldenhar syndrome. Comparisons may be useful for a differential diagnosis with Treacher Collins, **CHARGE**, Townes-Brocks syndromes and **VACTERL** association. *Treacher Collins syndrome* (TCS) is an extremely rare genetic disorder (mutations in the *TCOF* gene) characterized by distinctive abnormalities of the craniofacial area due to underdevelopment (hypoplasia) of certain portions of the skull (e.g., supraorbital rims and zygomatic arches) and lower jaw [40]. Opposite GS infants with TCS may also have hypoplastic and/or microtic outer ears with blind ending or atresia of external ear canals, conductive hearing loss. Infants with the disorder may have colobomas. **CHARGE** syndrome stands for coloboma, hear defect, atresia choanae (also known as choanal atresia), restricted growth and development, genital abnormality, and ear abnormality.[1] Signs and symptoms vary among people with this condition; however, infants often have multiple life-threatening medical conditions. The diagnosis of *CHARGE syndrome* is based on a combination of major and minor characteristics. In more than half of all cases, mutations in the *CHD7* gene cause **CHARGE** syndrome [41]. *VACTERL association*, a rare disorder resulting from fetal development defects, is characterized by con-

genital abnormalities affecting several organ systems. **VACTERL** is an acronym representing (V)ertebral abnormalities (like GS) including hemivertebrae and malformation of the lower vertebrae (sacrum); (A)nal atresia, a condition in which there is absence of the anal opening; (C)ardiac defects, particularly ventricular septal defects; (T)racheo(E)sophageal fistula; (R)enal abnormalities including absence of the kidney and hydronephrosis; and improper development of one of the forearm bones (radial dysplasia) and other (L)imb defects. *Townes-Brocks syndrome* associated with abnormalities tend to involve the face (hemifacial microsomia), ears (malformation of the outer ears, preauricular tags and/or pits, sensorineural hearing loss), arms (polydactyly, syndactyly) and legs (limbs), gastrointestinal system (rectovaginal or rectoperineal fistula), and kidneys (renal hypoplasia; vesicoureteral reflux). Diagnosis of Goldenhar, Treacher Collins, **CHARGE**, Townes-Brocks syndromes and **VACTERL** association are based on anomalies in the structure of the facial skull, but the combinations of anomalies found in this case are more in favor of Goldenhar syndrome, which was established after the refining examinations and differential diagnosis.

## CONCLUSIONS

This case demonstrates a rarely described association of oculo-auriculo-vertebral disorders, malformation of respiratory system (hypoplasia of the lower lobe of the left lung with relaxation of the left cupula of the diaphragm), heart abnormality (atrium septal defect).

## CONFLICT OF INTERESTS

There is no conflict of interests.

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