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Case Report

Oculo-auriculo-vertebral Spectrum (Goldenhar Syndrome): Presentation of Three Cases

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ABSTRACT

Background: The oculo-auriculo-vertebral spectrum (OAVS) includes three closely related rare congenital diseases of different severity with an incidence of 1/3500-7000 individuals. The involvement is usually unilateral; however, bilateral involvement may also occur. In addition to craniofacial anomalies, defects in the cardiovascular, genitourinary, vertebral, and central nervous systems can be observed as well. The phenotype of the cases is highly variable. Goldenhar syndrome is the most severe form of this condition.

Case report: In total, three instructive cases of Goldenhar syndrome with different features have been reported in the present case study. The most common ear anomalies among these three cases included external auditory canal atresia, helix deformities, preauricular skin tag and/or ear pitting, microtia, and conductive hearing loss. The second case was presented with hemifacial microsomia on the more severely affected right side, and the third case had bilateral Brushfield spots and a dermolipoma ophthalmological findings.

Conclusion: Based on the findings of the present study, OAVS should also be considered in the differential diagnosis of the cases with facial and ear anomalies.

Keywords: Congenital anomaly, Goldenhar syndrome, Hemifacial microsomia, Oculo-auriculo-vertebral disorder

Introduction

The oculo-auriculo-vertebral spectrum (OAVS, MIM:164210) is a developmental defect of the first and second branchial arch typically affecting the external and middle ear, mandible, temporomandibular joint, masticatory muscles, facial muscles, and other soft facial muscles. In some cases, the skull and neck, and other facial structures, such as the orbita, eyes, and nose are affected as well. The involvement is usually unilateral; however, bilateral involvement may also occur. Defects in the cardiovascular (CVS), genitourinary, vertebral, and central nervous systems can also be observed along with craniofacial anomalies. The phenotype of the cases is highly variable (1,2).

OAVS refers to three rare diseases that are believed to be closely related and represent different severity ranges of the same disorder. Although oculo-auriculo-vertebral disorder represents the mildest form of the spectrum, hemifacial microsomia and Goldenhar syndrome are considered the intermediate form and the most severe form of the spectrum (3). The incidence of the syndrome and the male-to-female ratio is 1/3500-7000 and 3:2, respectively (4). Although most cases of the condition are sporadic, familial cases with autosomal recessive or autosomal dominant inheritance have also been reported. It is believed that many environmental and genetic factors play a role in the occurrence of the syndrome of unknown etiology (5).

This study reports three instructive cases of Goldenhar syndrome with different features.

Case report

Case 1

The first case included a male baby born at 38th gestational weeks from the first pregnancy of a 23-year-old mother. His prenatal history revealed bilateral hydroureteronephrosis. On

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physical examination, the birth weight, height, and head circumference of the baby was obtained at 2300 g (3-10thcentile), 49 cm (25-50thcentile), and 34 cm (25-50thcentile), respectively. He had anotia, bilateral external ear canal atresia, broad nasal root, retrognathia, and polydactyly in the left hand (Figure 1A-C). The CVS examination revealed 1-2/6 murmur on pulmonary focus. There was an atrial septal defect (ASD) on echocardiography. No response was obtained in the brainstem auditory evoked potential (BAEP). Temporal bone computed tomography (CT) revealed bilateral external ear anomaly and bilateral stapes agenesis. Orbital magnetic resonance imaging was normal. Cranial ultrasonography and bone radiographs of the patient were all normal; however, urinary ultrasonography demonstrated a left multicystic dysplastic kidney. Chromosomal analysis revealed 46, XY karyotype.

Figure1. A) Absence of bilateral auricle; B) Atresia in the external auditory canals, broad nasal root, and retrognathia; C) Polydactyly (6 fingers) in the left hand in Case 1.

Accordingly, the patient was diagnosed with Goldenhar syndrome. He was discharged on the 13th day of his hospitalization with recommendations for outpatient follow-up. No information was obtained about him due to the fact that he did not refer to the polyclinic control.

Case 2

A female baby born from the fourth pregnancy of a 39-year-old mother at 37th gestational weeks by cesarean section. On physical examination, the birth weight, height, and head circumference were reported to be 1780 g (< 3rd centile), 42 cm (< 3rd centile), 34 cm (3-10th centile), respectively. She had bilateral helix deformity along with low-set ears, a preauricular skin tag, hemifacial microsomia on the right side, and micrognathia (Figure 1A, B). The CVS examination exhibited a 2/6 pansystolic murmur on the left edge of the sternum. Echocardiography revealed a patent ductus arteriosus (PDA) and peripheral pulmonary stenosis. Despite the normal hearing response in the right ear, no response was obtained from the left ear on otoacoustic emission/BAEP. The patient's cranial ultrasonography and bone radiographs were normal; however, urinary ultrasonography revealed left renal agenesis. Chromosomal analysis revealed 46, XX karyotype.

The patient was diagnosed with Goldenhar syndrome and discharged on the 17th day of her hospitalization with the recommendations for outpatient clinic follow-up. However, the case was not followed up, since she did not refer to the polyclinic control.

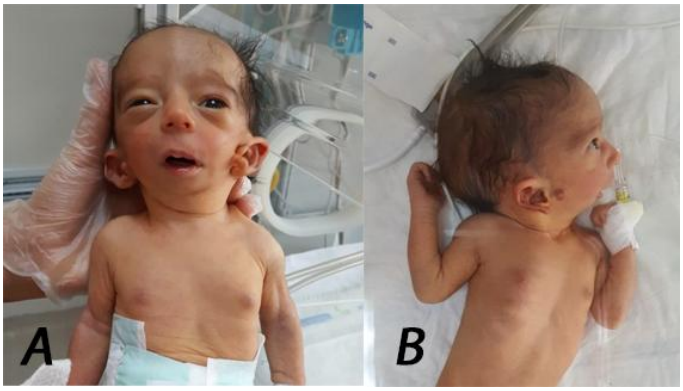

Figure 2. A) Bilateral low-set ears, helix deformity, and preauricular skin tags; B) Right-sided hemifacial microsomia and micrognathia.

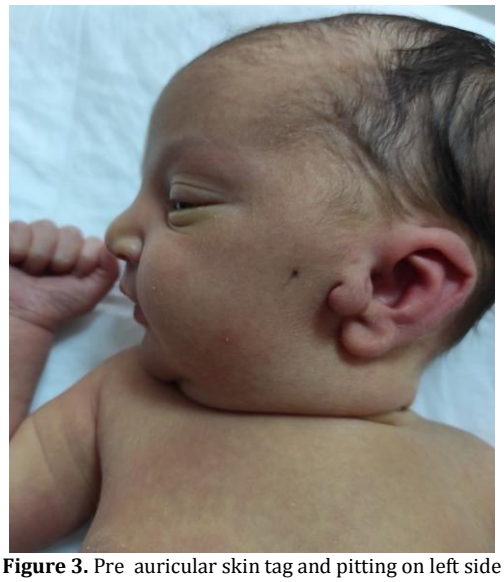

Figure 3. Pre auricular skin tag and pitting on left side

Case 3

A five-day-old girl, born by cesarean section at 38 weeks of gestation from the first pregnancy of a 27-year-old mother, presented with neonatal jaundice. On physical examination, the patient's birth weight, height, and head circumference were reported to be 3600 g (50-75th centile), 49 cm (25-50th centile), and 35 cm (50-75th centile). She had bilateral preauricular skin tags (two on the left, one on the right) and a helix anomaly. There was a broad nasal root, and preauricular pit on the left side (Figure 3). She also had bilateral external auditory canal atresia. Temporal bone CT demonstrated the bilateral external auditory canal atresia with normal middle and inner ear structures, except for rudimentary manubrium mallei. The patient did not pass the BAEP test. Ophthalmological examination revealed Brushfield spots and a dermolipoma on the left upper eyelid. Cranial and abdominal ultrasonography and radiographs did not show any additional anomalies. There was a patent foramen ovale (PFO) on echocardiography. Chromosomal analysis revealed 46, XX karyotype.

The patient's findings were indicative of Goldenhar syndrome. The patient was discharged on the 8th day of hospital stay after the treatment of jaundice. Otolaryngology recommended repetition of the hearing test at the age of three months and outpatient clinic control for hearing aids.

Discussion

Goldenhar syndrome is a rare multifactorial disease that varies greatly from case to case in terms of symptoms and signs. Although there is no consensus on the diagnostic criteria of the syndrome, hemifacial microsomia, anomalies of eye-ear and vertebra have been reported most frequently in these patients (2). A diagnosis of Goldenhar syndrome was made in three patients presented in this study, based on the classical findings of the disease.

Goldenhar syndrome is included in the axial mesodermal dysplasia spectrum. This disease group, which is observed as a combination of branchial, pulmonary, cardiovascular, gastrointestinal, renal, urogenital, and skeletal malformations is a primary developmental defect that occurs due to the issues related to mesodermal cell migration during the early blastogenesis period in the first four weeks of embryo development. This defect, which can extend to different craniocaudal levels can be called by different names, such as VACTERL association if it causes vertebral, anal, cardiac, tracheoesophageal, and renal anomalies; OAVS if it causes facial, vertebral, and ear anomalies; and MURCS association if it causes vertebral, genitourinary, renal anomalies [Mullerian duct aplasia (MU), renal aplasia (R), cervicothoracic somite dysplasia (CS)] (6,7).

Goldenhar syndrome is a disease with multifactorial inheritance, where genetic and environmental factors are thought to play a role in the etiology. Only 2% of the patients have a family history of Goldenhar syndrome. Maternal diabetes and adriamycin, retinoic acid, tamoxifen, cocaine, and thalidomide use in pregnancy are among the etiological factors (7). None of our patients had a maternal history of drug use and a known chronic disease. Moreover,

no karyotype anomaly was detected in the chromosomal analysis of the three cases.

The most common ear anomalies in Goldenhar syndrome include external auditory canal atresia, helix deformities, preauricular skin tag and/or ear pitting, microtia, and conductive hearing loss (8). Among the patients presented in this study, the first had anotia and external auditory canal atresia, the second had low-set ears, helix deformity, and preauricular skin tags, and the third had bilateral preauricular skin tags, external auditory canal atresia, and a preauricular pit of the left ear.

The main ophthalmological finding in patients with Goldenhar syndrome is epibulbar choristoma with an incidence rate of 30-60% (5). Other reported anomalies include amblyopia, strabismus, astigmatism, anophthalmia, microphthalmia, motility disorders, blepharoptosis, palpebral fissure, eyelid coloboma, coloboma of the iris or choroid, iris atrophy, polar cataracts, as well as anomalies of the lacrimal drainage system, retina, and optic nerve (9). Although the first two patients had no ocular findings, bilateral Brushfield spots and a dermolipoma was observed on the left upper eyelid in the third patient.

Different craniofacial findings reported in Goldenhar syndrome include mandibular hypoplasia, hypoplasia of facial muscles, facial paralysis, cleft lip and palate, high-arched palate, broad nasal root, micrognathia, and choanal atresia (7). Out of the three presented cases, the first and third had a broad nasal root, the second had facial asymmetry, and the third had a high-arched palate. Despite the bilateral helix anomaly in the second case, only the left inner and middle ear structures were affected, and the right ear hearing was normal. The third case had bilateral helix anomaly and the external auditory canal atresia as well. Hemifacial microsomia is usually seen on the side where the ear deformity is observed. Consistently, our second patient had hemifacial microsomia on the more severely affected right side.

Other system anomalies may accompany Goldenhar syndrome at the incidence rate of 50%. Cardiovascular anomalies, which can cause significant morbidity and mortality, also accompany this syndrome at a rate of 5-58%. Among the presented cases, the first had ASD, the second had PDA and peripheral pulmonary stenosis, and the third had PFO. Central nervous system anomalies also accompany Goldenhar syndrome at a rate of 12-47%. Other related anomalies include lipoma, hydrocephalus, meningomyelocele, teratoma, lissencephaly, holoprosencephaly, Arnold-Chiari malformation, corpus callosum agenesis, diffuse cerebral hypoplasia (10). However, cranial imaging of our three cases was normal. Vesicoureteral reflux, hydronephrosis, and ureteropelvic stenosis have been reported as genitourinary system anomalies (11). The left kidney of the first case was a multicystic dysplastic kidney, and left renal agenesis was detected in the second case, respectively.

Genetic disorders, such as Treacher-Collins syndrome, branchio-oto-renal syndrome, Townes Brocks syndrome, CHARGE syndrome, and VACTERL association should be considered in the differential diagnosis of Goldenhar syndrome (12). The current clinical and radiological findings of the three presented cases were consistent with the diagnosis of Goldenhar syndrome.

Based on the findings of the three presented cases, it is recommended that Goldenhar syndrome should also be considered in the differential diagnosis of cases with facial anomalies accompanied by ear anomalies. A multidisciplinary approach is necessary in these cases.

Conclusion

None.

Acknowledgments

None.

Conflicts of interest

None.

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