Intrauterine diagnosis and follow-up of a child with Goldenhar Syndrome: case report

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Abstract

Introduction: goldenhar syndrome is a rare congenital syndrome that affects the craniofacial morphogenesis. It is a complex syndrome, with heterogeneous presentation which the diagnosis can still be performed in the intrauterine through morphological ultrasound.

Description: a case report of a 4-year-old male patient diagnosed with Goldenhar syndrome, along with its clinical presentation, diagnostic investigation and follow-up.

Discussion: the follow-up on these patients remains a challenge, since it can affect different systems and with different presentations. The earlier the diagnosis is performed, the greater the patient's chances of having a favorable prognosis with multidisciplinary stimulation. The objective of this article is to contribute to the medical literature, in order to assist in the diagnosis and management of future cases.

Key words *Goldenhar syndrome, Oculoauriculovertebral syndrome, Hemifacial microsomia, Prenatal diagnosis*

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Introduction

Goldenhar syndrome is a congenital syndrome affecting craniofacial morphogenesis. It was initially described by an ophthalmologist Maurice Goldenhar in 1952, in view of the perceived association of the ocular, auricular and facial features. It was later revised by Robert J. Gorlin in 1963, who additionally described associated vertebral alterations. The syndrome is also known as Goldenhar-Gorlin syndrome or oculo-auriculo-vertebral spectrum (OAVS).[1] This latter term suggests the existence of a common phenotypic spectrum, but with the presence of a variable association between other malformations associated with the involvement of the first and second branchial arches.[1]

It is characterized by auricular involvement (anotia and microtia, pre-auricular appendages, blind fistulas with or without hearing loss), facial (hemifacial microsomia), ocular (dermoid and/or lipodermoid-epibulbar, microphthalmia) and vertebral alterations (hemivertebra, vertebral fusions and other malformations).[1,2] However, not limiting to these, central nervous, renal, cardiac and skeletal system involvement have already been described.[1] For this reason, some authors consider it as a variant of hemifacial microsomia, not being synonymous.[2] It is a rare syndrome, with an incidence between 1:3500 and 1:5600 live births, with a higher prevalence in males (3:2).[2]

The diagnosis and follow-up of these patients remain a challenge, since it can affect several systems and with varied presentation, requiring interprofessional follow-up to form an individualized care plan. In this paper we report a Goldenhar syndrome case, its clinical presentation, diagnostic investigation and evolution. The aim of this work is to contribute to the medical literature, in order to assist in the diagnosis and management of future cases.

Case description

A four-year-old mixed colored male patient, born in Recife, PE, had a followed up in a General Pediatrics outpatient clinic. The probable diagnosis of Goldenhar syndrome was received in the intrauterine and confirmed during post-natal follow-up.

The mother reported a diagnosis of gestational diabetes, with good control with a diet, but denied other pathologies, exposures or other events during pregnancy. No family history of craniofacial abnormalities.

During prenatal follow-up, she underwent morphologic ultrasonography at the gestational age of 24 weeks and five days, identifying cleft lip and palate on the right; preauricular appendix on the left; prenasal thickening; hypoplastic right nasal bone; slight pericardial effusion; moderate ascites and clawed hands. Since then, the baby was followed up by a fetal medicine team.

In view of these findings, chromosomal or genetic syndrome were initially suggested as diagnostic hypotheses. Further investigation was carried out with molecular chromosomal study, with no molecular evidence of significant chromosomal alterations identified, in addition to chromosomal study of amniotic fluid not detecting triploidies or aneuploidies tested (13,18, 21, X and Y). It was suggested to proceed with a microRNA study, but due to the high financial cost and low sensitivity of the test, it was decided not to perform it.

Fetal echocardiogram identified minimal ostium primum atrial septal defect with right-to-left shunt, minimal perimembranous ventricular septal defect, extrasystoles, but no hemodynamic repercussions.

Weekly ultrasonography were performed, which showed involution of ascites, with maintenance of other findings. As the diagnostic hypotheses of both chromosomal and genetic syndrome were ruled out, the main hypothesis, from then on was Goldenhar syndrome in view of the sonographic findings.

The mother presented polyhydramnios, due to maternal gestational diabetes and cleft palate, associated with poor swallowing of amniotic fluid.

Patient was born by cesarean section at 38 weeks and five days with good vitality. He was followed early by a multidisciplinary team.

At six months of age, the patient underwent a CT scan of the skull and dorsal column to evaluate the possibility of surgical correction of the cleft palate and other malformations. Examination showed anomaly of segmentation of the vertebral body at T6, assuming aspect of "butterfly vertebra".

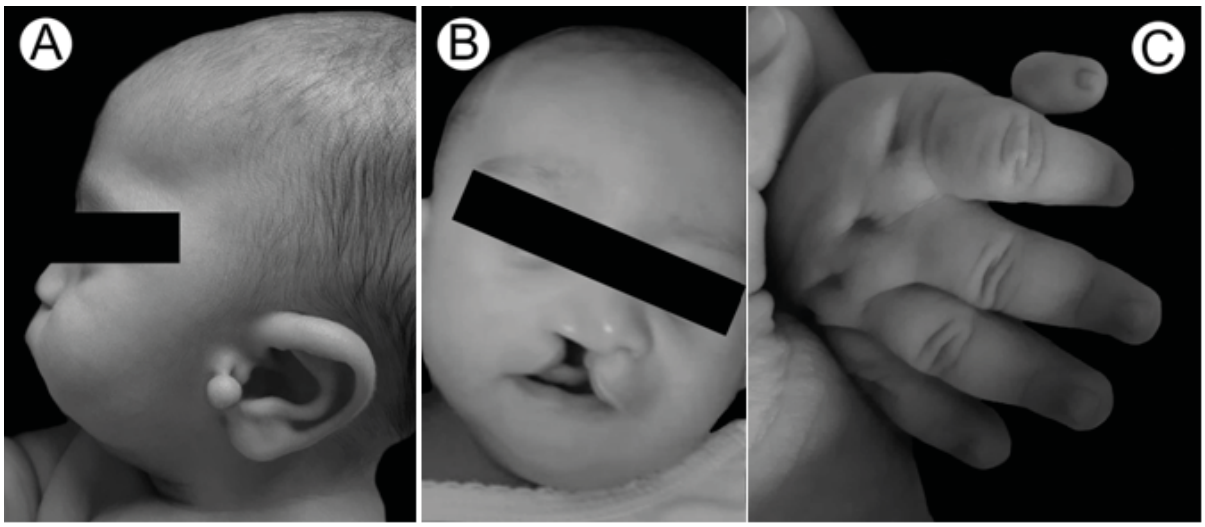
He underwent cleft lip and palate correction surgery, removal of pre-auricular appendix and amputation of the 1st chirodactyl on the right (Figure 1).

In periodic ophthalmologic follow-up, visual acuity below the expected for the age group was identified, with subnormal vision; pendular nystagmus, divergent dyskinetic strabismus, and with visual evoked potential suggestive of delayed visual impulse transmission. In addition to the moderate degree of astigmatism, requiring corrective lenses. Visual stimulation and occupational therapy were performed under pediatric bobath method, bobath baby and visual area.

The patient also maintained follow-ups on speech therapy and physiotherapy, evolving with regular neurodevelopment, without impairment of milestones development, having no other deficits.

Figure 1

Photos of the patient showing (A) auricular appendage on the left and mandibular hypoplasia, (B) Cleft lip and palate, (C) rudimentary 1st finger and pedicle on the right.



Discussion

Goldenhar syndrome, or oculo-auriculo-vertebral spectrum (OAVS), is a congenital disorder of craniofacial morphogenesis, characterized by the presence of the classical clinical triad: ocular, auricular and vertebral alterations.[1,2]

The most prevalent findings in patients with this syndrome are: epibulbar lipodermoids, microtia, hemifacial microsomia, preauricular appendages and fistulas, vertebral anomalies, hypoplasia of several bones such as maxilla, mandible, zygomatic arch and malar area, cleft lip, cleft palate, mandibular protrusion and malocclusions. They may also exhibit multisystemic alterations such as cardiac, renal, gastrointestinal and central nervous system, as well as cognitive deficit and global developmental delay.[2-5]

The occurrence of this syndrome is more often sporadic, but it may involve the relationship of genetic and environmental factors. In some cases, in which family inheritance pattern is perceived, it behaves as an autosomal dominant disorder, with several chromosomal abnormalities already being observed, among which the most common is the deletion of 5p15.33-pter; there may also be deletion of the 12p13.33 region involving the WNT5B gene, partially overlapping micro duplications in 14q23.1; aneuploidy in the X chromosome.[1,6]

The risk factors involved are diabetes mellitus during pregnancy, twin or multiple pregnancies, assisted reproduction techniques, hormonal therapy, exposure to tamoxifen, thalidomide, smoking and advanced age.[2,3]

In relation to its pathophysiology, the most accepted hypothesis is that there is a disturbance in the development of the first and second branchial arches, due to a reduction in blood supply or a focal hemorrhage in this region. Another hypothesis is that there is a defect in the formation, migration, proliferation and survival of neural crest cells, which are responsible for the formation of craniofacial regions.[1,2,3,7]

The diagnosis of Goldenhar syndrome is eminently clinical, but complementary tests can help in the process. Diagnosis can be made in intrauterine, as in the case described, by fetal ultrasonography that can detect microtia, preauricular appendages, mandibular hypoplasia, microphthalmia, orbital hypoplasia, cleft palate or through genetic studies.[2,7,8]

Ultrasonography is a non-invasive, safe prenatal diagnostic test usually used in the investigation of fetal malformations in clinical practice. It is indicated to attempt at least minimal assessment of the fetal face, usually including assessment of the upper lip and, when possible, other structures such as the nose and orbit. The evaluation of cleft palate in this method, sometimes difficult, can be facilitated with the evaluation of the retronasal triangle, being expected when there is a cleft present, the presence of abnormal configuration of this structure.[9]

Nuclear magnetic resonance imaging (MRI) is also a non-invasive, highly accurate, safe method that can be used in this investigation, but it is still expensive and not always available.[9]

In case of suspicion of chromosomal defects, based on alterations found in morphological screening, the investigation can be continued by non-invasive methods such as the study of free fetal DNA in maternal blood. This test has good sensitivity, but in case of alterations it is necessary to continue the investigation by invasive methods such as amniocentesis, chorionic villus sampling, cordocentesis or fetoscopy with tissue biopsy.[9]

Objective criteria can be used to assist in the diagnosis of Goldenhar syndrome, such as those adopted by Strämland *et al*.[10] who establish the diagnosis when there are two or more clinical features in the orocraniofacial, ocular, auricular and vertebral regions.[3]

Other criteria are also described in the literature, such as those proposed by Digilio *et al*.[11] suggesting the diagnosis when at least two of these findings are present: unilateral microtia, unilateral mandibular hypoplasia, epibulbar dermoid cysts (unilateral or bilateral) or vertebral malformations.[3]

Goldenhar syndrome has a wide differential diagnosis with Parry Romberg syndrome (PRS), hemifacial microsomia, Townes-Brocks syndrome and branchiopoto-renal syndrome. Table 1 describes the main differences that allow differentiation between these syndromes.[8]

Oral and maxillofacial disorders are usually unilateral, but may present bilaterally. These variations include macrostomia, cleft lip, cleft palate, facial paralysis, micrognathia/retrognathia, salivary gland agenesis with appearance of fistulas, masseter, temporal and pterygoid atrophy or hypoplasia, pharyngeal anomaly and tracheoesophageal fistula.[1-3]

In the case described, the patient had cleft palate on the right, associated with hypoplastic right nasal bone, mandibular hypoplasia, alterations that, depending on the type and severity, can generate difficulties in the routine, especially for the newborn, both for speech development and feeding. Exclusive breastfeeding up to the sixth month is a protective factor against infections and anemia; therefore, a child born with difficulty in maintaining this protective parameter needs multidisciplinary monitoring aimed at assisting him/her and his/her family to promote a better quality of life until this problem is corrected.[12]

Moreover, these same alterations can generate communication problems, even when cognitive functioning is adequate for age, since it generates articulation disorders and consequently some morphosyntactic skills are altered. Corrective surgery also has an aesthetic objective.[13]

About 50% of the patients with Goldenhar syndrome have ocular alterations. The main alterations are dermoid, epibulbar, lipodermoid and upper eyelid coloboma. Other alterations are subconjunctival or anterior orbital dermolipoma, ptosis, strabismus, atrophic cataract, enophthalmos, microphthalmia and anophthalmia.[1,2,14]

According to Rooijers *et al*.,[14] the incidence of severe visual impairment is present in about 7.7 to 30% of the patients. Thus, ophthalmologic evaluation becomes mandatory in all cases of Goldenhar syndrome, requiring visual acuity tests, eye movements, strabismus evaluation, examination of eyelids and appendages, ocular surface, anterior and posterior segment examination, and gonioscopy for angle evaluation. Coloboma is a surgical emergency, requiring early correction to preserve vision.[2,15]

The reported patient has visual acuity below the expected for the age group, with low vision; pendular nystagmus, divergent dyskinetic strabismus, and with visual evoked potential suggestive of delayed visual impulse transmission. In addition to moderate degree of astigmatism.

Ophthalmologic follow-up of these patients is extremely important, as they can reduce the rates of amblyopia, resulting from abnormal stimulation of vision during early childhood.[1]

Regarding to auricular alterations, according to Martelli-Júnior *et al*.,[5] pre-auricular appendages are the most commonly found conditions. In addition, deformities of the inner, middle and outer ear can be found, resulting in partial or total hearing loss.[1,5] Middle ear abnormalities include reduced cavity size and fusion between the hammer and anvil bones. Middle ear vestibular organ defects have also been documented.

In the patient studied, a left preauricular appendage was observed, but no hearing acuity loss was detected.

Vertebral anomalies are most frequent in the cervical region, followed by the thoracic spine and ribs. The main abnormalities include presence of hemivertebra, block vertebra, scoliosis/kyphoscoliosis and spina bifida.[9,16] In the case presented, presence of hemivertebra at T6 was observed. In addition, extremity abnormalities such as partial or total absence of the radius and abnormalities of the thumbs are also common,[17] so that a rudimentary 1st chirodactyl and pedicle on the right were found in the case described.

The frequency of cardiovascular malformations in Goldenhar syndrome ranges from 5 to 58%, according to Palheta Neto *et al*.,[18] with tetralogy of Fallot being one of the most frequent. Nevertheless, intraventricular communication with pulmonary atresia (IVC + PA), transposition of great arteries (TGA) and double inflow tract to the left ventricle are also manifestations evidenced in this syndrome. Septal defects, which include ostium secundum-type interatrial communication and intraventricular communication are the second most prevalent type of cardiac manifestations. Other alterations evidenced are patent ductus arteriosus, atrioventricular septal defect, pulmonary artery stenosis and cor triatriatum. Among these manifestations, IVC + PA, double inflow tract to the left ventricle, atrioventricular septal defect and cor triatriatum are the most associated with cardiac surgery and death in the first two years of life. Therefore, it is extremely important to recognize these cardiac alterations in the prenatal period so that there are measures to improve the prognosis of patients.[15]

Table 1

Table with differential diagnosis in relation to Goldenhar Syndrome.

	Goldenhar Syndrome	Hemifacial Microsomia	Treacher Collins Syndrome	Branchiopoto-renal syndrome
Incidence	1/3,500–1/26,550	1/3,500–1/26,550	1/50,000	1/40,000
Etiology	Multifactorial	Multifactorial	Loss of TC0F1 gene function on chromosome 5	Most common: EYA1 gene mutation Other: SIX1 and SIX 5 mutations
Most common type of hearing loss	Conductive	Conductive	Conductive	Conductive, sensorineural or mixed
Unilateral or bilateral facial deformity	Usually unilateral	Usually unilateral	Usually bilateral	Not applicable
Ocular alterations	Epibulbar dermoids, upper eyelid colobomas, microphthalmia, anophthalmia, ptose palpebral	Similar to Goldenhar syndrome but without epibulbar dermoids	Lower eyelid colobomas, missing medial lower eyelashes, downward tilt of palpebral fissures, affected vision, skeletal dysmorphism of orbits.	None
Auricular alterations	Microtia, acrochordons atresia/stenosis of the external acoustic meatus, absence of auricle, anotia, preauricular fossae/ sinuses, middle ear malformation and inner ear malformation are less common	Similar to Goldenhar syndrome and occur in 65-99% of the patients	Deformed external ear, microtia or anotia, stenosis or atresia of the external acoustic meatus, deformed tympanic membrane	75-85% of cases: Preauricular fossae Other: preauricular appendages, bat ears, microtia, atretic external auditory canal; abnormal ossicles, facial nerve and fallopian canals; hypoplastic cochlea and absent or hypoplastic semicircular canals
Craniofacial alterations	Mandibular hypoplasia, mandibular ramus asymmetry, maxillary and malar hypoplasia, TMJ abnormalities, micrognathia, cleft palate with or without cleft lip	Similar to Goldenhar syndrome	Most common: Malar hypoplasia, Other: mandibular and maxillary hypoplasia, micrognathia, retrognathia, cleft palate	High arched or cleft palate, deep overbite
Other musculoskeletal alterations	Vertebral defects, clubbing, polydactyly, clinodactyly, camptodactyly or single palmar fold	No vertebral defects	Rare vertebral defects	None
Associated alterations	Cardiac, renal, genital, gastrointestinal, may have some cognitive impairment	Similar to Goldenhar syndrome	Cardiac, renal, cryptorchidism, airway abnormalities	Aplasia or stenosis of the lacrimal ducts
Additional alterations				Renal dysplasia in more than 2/3 of cases, branchial fistulas (usually bilaterally in the lower neck)

Adapted by Kabak SL *et al.*[8]

Considering not only cardiological alterations, but also a wide variety of anomalies that may affect the patient, this may lead to developmental alterations.[3,13] Therefore, the recommended treatment should be individual with a multidisciplinary and interdisciplinary approach in order to improve not only the functionality but also the patient's aesthetics.[13] This approach allows timely interventions to be performed, providing better benefit to the patient, as occurred in the case reported here. This follow-up was essential for this child to have regular psychosocial development, without compromising his milestones development.

Authors' contribution

Lima VFS and Pinto BAT: conception of the idea, data collection and analysis, writing and review of the manuscript. Nelson CBL, Campos ED, Gonsioroski LP, Souza MRS and Siqueira RCC: data analysis, drafting and revising the manuscript. Vilarim JNA: conception of the idea, supervision and revision of the manuscript. All authors approved the final version of the article and declare no conflict of interest.

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