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Review Article

Goldenhar Syndrome – A Literature Review

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Abstract

Golden har syndrome is a hereditary condition which is characterized by preauricular appendages, fistulas, and epibulbar dermoids. It not only involves the facial structures, but also includes renal, genitourinary, cardiac, and skeletal anomalies. The aetiology of the syndrome is not fully understood however many hypothesis have been proposed and described. The incidence varies from 1 in 3,500 to 1 in 5,600 live births. Males are more commonly affected by the syndrome than females, the ratio being 3:2. It can be both unilateral and bilateral, however involvement of the right ear is more common. The diagnosis should be based on the clinical aspect of the syndrome which should further be associated with radiological findings and systemic conditions. For diagnosisto be confirmed the subject should at least have microtia and preauricular, or auricular abnormalities. Treatment of deformities requiresmultiple procedures performed by a multidisciplinaryteam of doctors, and a long-term regular follow-up is also important tomonitor the growth and development of the patient.

INTRODUCTION

Goldenhar syndrome was first observed by Canton in 1861, and later by Von Arlt, in 1881, however it went unnoticed [1,2]. Maurice Golden har, the Swiss ophthalmologist in 1952 recorded three new cases in addition to the sixteen previously recorded and first described the syndrome in detail thus it came to be known as Goldenhar syndrome [3]. It consisted of preauricular appendages, fistulas, and epibulbar dermoids [4].In 1960s, hemifacial microsomia was a prevalent condition which used to affect aural, oral, and mandibular development. It had both unilateral and bilateral involvement. Golden har syndrome is considered to be a variant of hemifacial microsomia, characterized additionally by vertebral anomalies and epibulbar dermoids [1]. Gorlin et al. in 1963, included vertebral anomalies also as one of the manifestations of this syndrome and thus suggested the name Oculoauriculo vertebral (OAV) dysplasia [4,5]. Smith in 1978 used the term facio-auriculo-vertebral sequence to include both Goldenhar syndrome and Hemifacialmicrosomia [4,5].

It is a rare hereditary condition characterized by numerous anomalies affecting the first and second branchial arches of the first pharyngeal pouch, the first branchial cleft, and the primordia of the temporal bone [4,6] before the end of organogenetic period (7^{th} or 8^{th} week of embryonic life) [7].It is also known as Goldenhar-Gorlin syndrome, facio-auriculo-vertebral dysplasia, unilateral craniofacial microsomia, first arch syndrome, first and second branchial arch syndrome, lateral facial dysplasia, velo-cardio-facial syndrome, otomandibular dysostosis, unilateral mandibulo facial dysostosis, unilateral intrauterine facial necrosis, auriculo-branchiogenic dysplasia, facio-auriculo-vertebral malformation complex [1,4]. The aetiology of this rare disease is not fully understood. However numerous hypotheses have been proposed to explain the etiopathogenesis of this syndrome. Gorlin and Pindborg 1964, suggested that some abnormal process affects the mesoblasts embryologically which affects the branchial and vertebral systems thereby resulting in the syndrome. However, the primary cause of this faulty embryological development is unknown [3]. Krause in 1970, suggested hereditary pattern to be the causative agent as he described the syndrome affecting a brother and sister [3].Jong bloet in 1971, suggested that Goldenhar's syndrome may be a result of fertilization of an overripe ovum, as he quotes the work of Witschi (1952) which showed the teratogenic effect of ageing on frogs' eggs before fertilization[3].Baum and Feingold in 1973, stated that Goldenhar's syndrome may be a sporadic event that occurs early in embryogenesis which is explained by reduced penetrance, somatic mosaicism or epigenetic changes [6,8,9].Also there are reports of familial cases in successive generation having history of consanguineous marriage that thus requires consideration of autosomal recessive, dominant, or multi factorial inheritance [4,5,10]. Multiple chromosomal anomalies have been linked to this complex, the most significant of which are 3del(5p) , del(6q),

trisomy 7 mosaicism , del(8q) (161),trisomy 9 mosaicism (166), trisomy 18 (14,58), recombinant chromosome 18 , del(18q) , ring 21 chromosome , del(22q) , dup(22q) , trisomy 22 , 49,XXXXX , 49,XXXXY and 47,XXY [1,10].

Poswillo in 1976, using an animal model, showed and suggested that maternal fetal hypoxia, hypertension, and anticoagulants can result into a hematoma in the region of the ear and jaw which expands and causes destruction of differentiating tissue which in turn can lead to branchial arch dysplasia. The degree of local destruction defines the severity of dysplasia which thus explains the variability of expression of the syndrome [4,10]. Gomez et al. in 1984 hypothesized about the role of radiologic intervention like cholecystography which is practised between the fourth and sixth weeks of pregnancy as a causative factor of the syndrome [4]. Lammer and Opitz, in 1986 suggested that hemifacial microsomia and OAVS may be a malformation sequence as a result of involvement of major primary neural crest cell in all or most cases which leads to its death along with the death of adjacent cell populations of the second arch and a retarded neural crest cell migration which is related to an altered retinoic acid (RA) and cellular retinoic acid binding protein (CRABPI) sensitivity in these cell populations [11-13].

Disturbance in chondrogenesis has also been suggested as a theory. A common pathway for CHARGE association and OAV spectrum has been proposed. Also the OAV phenotype has been noted in infants with diabetic embryopathy [1]. Goldenhar syndrome has also been observed in the children of diabetic mothers [14], and those exposed to cocaine, retinoic acid, thalidomide, tamoxifenprimido neteratological agents [10,15]. Also malnutrition, tobacco, andherbicides can result in congenital malformations as they are able to produce free radicals which may break the DNA [1].

The incidence varies from 1 in 3,500 to 1 in 5,600 live births [16]. It has a male predominance, the ratio being 3:2. Majority of cases are unilateral (85%) as compared to both sides (10 % to 33%). The right side ear involvement is being more common [3].

Facies

Unilateral macrostomia and marked facial asymmetry is present because of both displacement and abnormality of the pinna and other underlying abnormalities of skeleton. Aplasia or hypoplasia of the mandibular ramus and condyle may lead to reduction in the size of maxillary, temporal, and malar bones. Hypoplasia of the zygomatic area is also seen. Mild pneumatization of the mastoid region can be seen in few patients. Prominent forehead and frontal bossing is noticed during birth however it becomes less apparent with age [1,17,18].

Eye

Epidermoid tumors occur in 35 % of all cases. They can be Unilateral (50%) and bilateral (25%). They appear as solid yellowish or pinkish white ovoid masses varying in size from that of a pinhead to 8–10 mm in diameter. They occur most often at the inferotemporal quadrant at the limbus. The surface is usually smooth and frequently has fine hairs. They can occur at any location on the globe or in the orbit and can be dermoid (white solid masses), lipo-dermoid(25%) (yellow, movable, conjunctival), or dermis-like or complex (mesoectodermal). Astigmatism and lipid infiltration of the cornea can lead to encroachment on the pupillary axis leading to vision impairment. Other features include unilateral or bilateral blepharoptosis, elevated orbit, clinical anophthalmia or microphthalmia, retinal abnormalities, Colobomas of the upper eyelid, iris, chorioidea, and retina, ocular motility disorders (esotropia, exotropia , duane syndrome), microphthalmia, anophthalmia, cataract, antimongoloid obliquity of palpebral fissures, microcornea and congenital cystic eye [12,14,17,19, 20].

Ear

The patients have anotia to an ill-defined mass of tissue that is displaced anteriorly and inferiorly, to a mildly dysmorphic ear. Occasionally, anomalous pinnae are seen bilaterally. Supernumerary ear tags, unilateral and bilateral preauricular tags of skin and cartilage, along withblind fistulas and sinuses are extremely common. Narrow external auditory canals and atretic canals are found. Isolated microtia is considered a microform of OAV spectrum. There are lesions present in the middle and external ears which results in both conductive and sensorineural hearing loss. Aberrant facial nerves, patulous or absent eustachian tube and other external ear malformations (dysplasias, asymmetries, aplasias, and atresias of the external meatus); middle and internal ear anomalies are frequently present [1,21-23].

Central nervous system

Mental retardation and mental deficiency is seen. Nearly all cranial nerves are involved. There is abnormal course of the seventh cranial nerve and unilateral aplasia of the Trigeminal nuclei and the facial nerve as well as trigeminal anesthesia. Intracranial anomalies may include occipital and frontal encephaloceles, hydrocephaly, lipoma of corpus callosum, dermoid cyst, teratoma, Arnold- Chiari malformation, lissencephaly, arachnoid cyst, holoprosencephaly, porencephalic cyst, unilateral arhinencephaly, and hypoplasia of the corpus callosum [1,3,24].

Trachea and Lung

Tracheo-esophageal fistula is commonly seen. Pulmonary anomalies may range from incomplete lobulation to hypoplasia to agenesis, unilateral or bilateral, the absent lung usually is ipsilateral to the facial anomalies [1].

Heart

Congenital heart disease (ventricular septal defects), and tetralogy of Fallot with or without right aortic arch are very commonly seen. There is transposition of the great vessels. Tubular hypoplasia of the aortic arch associated with mild coarctation of the aorta along with cardiomegaly. Rare isolation of the left innominate artery with bilateral PDA pulmonary stenosis, dextrocardia, hypoplasia of the external carotid artery and situs ambiguous can also be observed [21,25, 26].

Skeletal alterations

Skull defects like cranium bifidum, microcephaly, dolichocephaly, plagiocephaly have been noted. Facial anteroposterior and vertical dimensions are reduced on the

affected side, especially in the lower face toward the otocephalic center. Cervical spine, cranial base anomalies and torticollis occur with increased frequency.The temporomandibular joint is anteroinferiorly displaced. Cervical vertebral fusions occur in as many as 60%, whereas platybasia and occipitalization of the atlas are found in approximately 30%. Spina bifida, hemi vertebrae, butterfly, fused and hypoplastic vertebrae, Klippel-Feil anomaly, MURCS association, scoliosis, and anomalous ribs (agenesis, bifidity, fusion, supernumerary) occur in most of the cases. Radial limb anomalies may take the form of hypoplasia or aplasia of radius and/or thumb and bifid or digitalized thumb. Vertebral column anomalies atlas occipitalization, synosto-sis, hemivertebrae, fused vertebrae, scoliosis, and bifid spine are also common [1,4,24,27].

Kidney & Gastrointestinal anomalies

Kidney may be absent, or can have double ureter, crossed renal ectopia, anomalous blood supply to the kidney, hydronephrosis, hydroureter are common. Anomalies of the urogenital system, uretropelvic junction obstruction, and imperforateanus with or without rectovaginal fistula can be seen [1, 28].

Oral manifestations

Dentofacial anomalies may include cleft lip and palate,tongue cleft, unilateral tongue hypoplasia, a highlyarched palate, hypoplasia of the maxillary and mandibular arches, micrognathia, gingival hypertrophy, super numerary teeth, enamel and dentin malformations, and delayed tooth development are common. Some patients often exhibit asymmetric development of masticatory muscles and agenesis of salivary glands or salivary fistulas. Velopharyngeal insufficiency has been seen [1,4,5,25,29].

The clinician should be able to differentiate the syndrome with the following malformations and syndromes that are also derived from aberrations in thefirst and second branchial arches during embryonic development like Treacher-Collins syndrome and Wildervanck syndrome (syndromacervicooculoacusticum), Variant of hemifacial microsomia, OAV spectrum, or OAV dysplasia , Mandibulo facial dysostosis, Townes-Brocks syndrome, the branchio-oto- renal (BOR) syndrome, maxillofacial dysostosis, nageracrofacial dysostosis, postaxial acrofacial dysostosis, characteristics of the VATER association (vertebral anomalies, ventricular septal defect, anal atresia, T-E fistula with esophageal atresia, and radial and renal dysplasia), CHARGE association (coloboma, heart disease, atresia choanae, retarded growth and development, genital anomalies, and ear anomalies and/or hearing loss), MURCS association (Mullerian duct aplasia, renal aplasia, and cervicothoracic somite vertebral dysplasia) overlap with the OAV spectrum and various first arch syndromes [1,4, 30].

Various diagnostic aids such as ultrasonography, computed tomography and radiographic analysis should done to rule out the syndrome. Ultrasonography is done during pregnancy and can rule out severehypoplasia of mandible, severe abnormality of the auricle, and cleft lipand/or cleft palate. Computed tomography is done for the evaluation of hearing to see the middle ear bones and to rule out skeletal findings radiographic analysis can be carried out [5].

The effect of Goldenhar syndrome is more evident as the child grows, because of delays in the growth and development of the affected areas [5].At birth, functional concerns in OAVS are the patency and adequacy of the airway, swallowing and feeding, hearing, vision, and the presence of other malformations that may have systemic implications [10].

Airway and oxygenation monitoring are essential. Airway problems can be treated by infant positioning, nasopharyngeal airway placement, tongue–lip adhesion, distraction osteogenesis to advance the mandible, or tracheotomy.Feeding difficulties are dealt with nasogastric feeds or the placement of a gastrostomy tube to maintain a positive nitrogen balance while allowing sufficient oxygenation. Posnick states that the most favourable functional and aesthetic results are obtained when surgery is carried out at or close to skeletal maturity, ideally when carried out with coordinated orthodontic therapy [10].

Timing of the primary and secondary reconstructions plays an important role in the complex treatment. Primary reconstruction consists of a cleft repair, corrections of colobomas and ear deformities, and extirpation of the dermoids and preauricular tags [4]. The extent of the temporomandibular joint (TMJ) dysmorphology is a principal factor when considering the timing of and techniques for mandibular reconstruction [10]. There are several methods of surgical treatment, such as conventional surgical procedures (costochondral rib graft and classical osteotomy) and the distraction technique. Using the distraction technique, it is possible to lengthen the jaw and the ramus of the mandible to the desired size; however, this technique does not result in normal growth and function of the temporomandibular joint. However, multiple-organ involvement can limit the surgical correction of the deformities and affect the management of patients with Goldenhar syndrome [4, 31].

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