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Cranial Defects in the Goldenhar Syndrome

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Four patients are presented with the Goldenhar syndrome (GS) and cranial defects consisting of plagiocephaly, microcephaly, skull defects, or intracranial dermoid cysts. Twelve cases from the literature add hydrocephalus, encephalocele, and arhinencephaly to a growing list of brain anomalies in GS. As a group, these patients emphasize the variability of GS and the increased risk for developmental retardation with multiple, severe, or unusual manifestations. The temporal relation of proposed teratogenic events in GS provides an opportunity to reconstruct biological relationships within the 3–5-week human embryo.

Key words: Goldenhar syndrome, cranial defects, oculoauriculovertebral "dysplasia", mandibulofacial dysostosis, hemifacial microsomia

INTRODUCTION

Since the description of three patients with epibulbar dermoids, preauricular appendages, and mandibular hypoplasia [Goldenhar, 1952], the variety and variability of anomalies associated with Goldenhar syndrome (GS) have been increasingly appreciated [Setzer et al, 1981]. Gorlin et al [1963] added vertebral defects to the spectrum of anomalies in GS, while others [Opitz and Faith, 1969; Greenwood et al, 1974; Feingold and Baum, 1978] have reported diverse ocular, skeletal, cardiac, and visceral defects. Because of the sporadic and heterogenous nature of GS, the prognosis of affected patients must be individually established by the anticipation and documentation of component anomalies. My purpose here is to review patients with GS and cranial defects and to emphasize the importance of cranial evaluation for selected GS patients. This report was stimulated by two GS patients with intracranial dermoids (cases 1 and 2) whose clinical course was more severe than originally predicted.

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An issue that complicates understanding of GS is its unclear relationship to more isolated forms of lateral facial dysplasia [Grabb, 1965; Ross, 1975], including hemifacial microsomia [Pashayan et al, 1970; Cohen, 1971; Thomas, 1980]. Isolated hemifacial microsomia can be viewed as a malformation [Spranger et al, 1982] involving the first and second branchial arches. However, when part of a malformation syndrome, hemifacial microsomia may be seen with the same variable pattern of ocular, cardiac, renal, radial, and vertebral anomalies described for GS. I therefore include in this series of cranial defects any patient having characteristic auricular plus mandibular or ocular defects that cannot be explained as unilateral malformation. Recognized Mendelian [Herrmann and Opitz, 1969; Summitt, 1969] or chromosomal disorders [Hodes et al, 1981] involving branchial arch defects are excluded.The series comprises four patients from a total of eight GS patients observed by our pediatric genetics service over the past 5 yr and 12 case reports gathered by survey of literature published after 1952.

CLINICAL REPORT

Patient 1

The patient was a 2.2 kg girl born 36 wk after an uncomplicated pregnancy to a gravida 1 25-year-old white woman. The family history was unremarkable. Examination (Fig. 1A,B) showed plagiocephaly, right hemifacial microsomia, bilateral cleft of lip and palate, micrognathia, hypoplastic and malformed right ear, preauricular

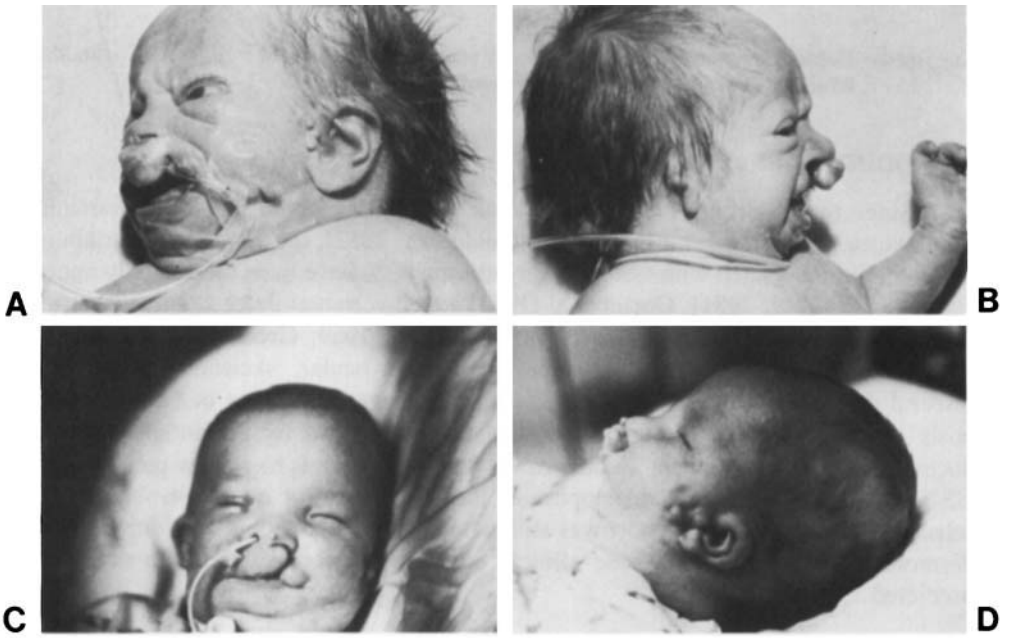

Fig. 1. (A) Patient 1, the left frontal view shows skin tags on the cheek and chest and a hypoplastic tragus; (B) patient 1, right lateral view; the apparent mass posterior to the neck is a skin fold; (C) patient 2, the frontal view shows a skin tag on the nose, cleft lip, and malformed ears; (D) patient 2, left lateral view.

and anterior cervical cartilaginous tags bilaterally, absence of right external auditory meatus, a lipoepidermoid cyst in the lower outer quadrant, a coloboma of the outer upper lid on the left, and absence of the left thumb. Skull films showed occipital intracranial calcification and chest roentgenograms demonstrated dextrocardia, hemivertebrae at T5-T7, scoliosis, and corresponding rib anomalies. CT scan showed cerebellar hypoplasia with a mass interpreted as a lipoepidermoid cyst of the posterior corpus callosum (Fig. 2A). She had a normal 46,XX chromosome constitution. She had neonatal feeding problems, failure to thrive, and chronic keratitis requiring bilateral tarsorrhaphy. Repair of the lip and palate clefts failed several times owing to

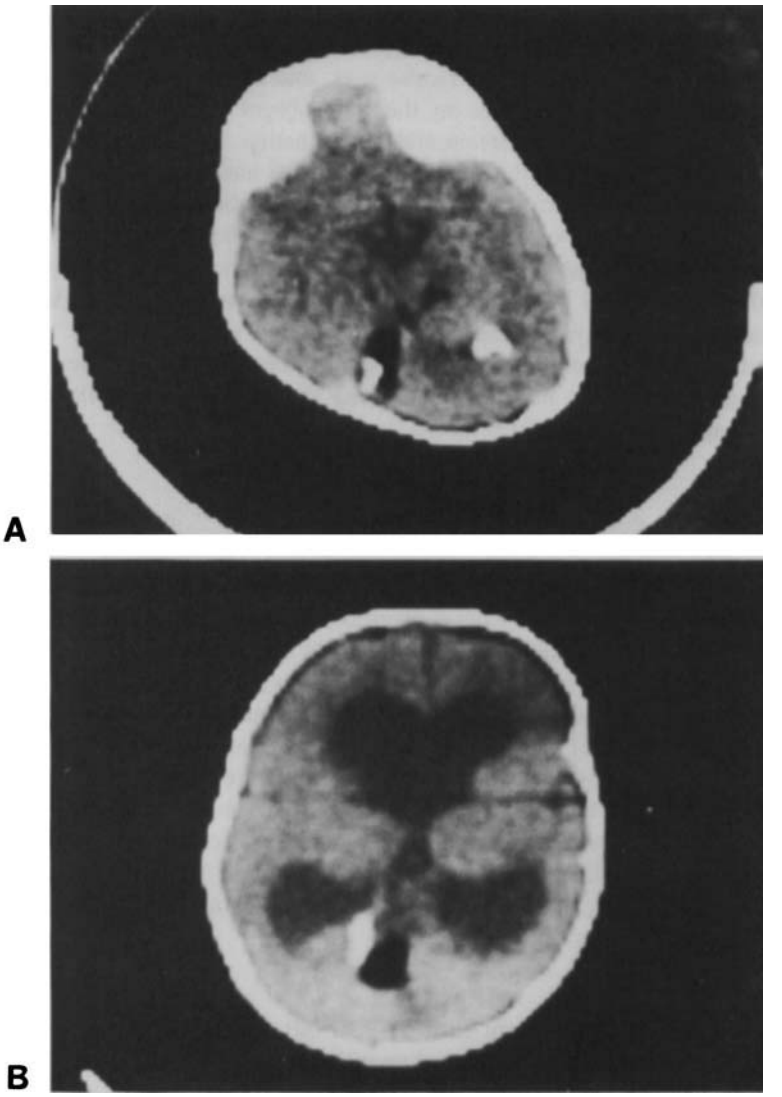

Fig. 2. CT Scans of patient 1(A) and patient 2(B) showing occipital masses with densities characteristic of fat and bone.

poor healing, but was eventually successful. A hearing loss was documented and treated with hearing aid. At 17 mo the girl had a length, occipitofrontal head circumference (OFC), and developmental level appropriate for five months and a weight appropriate for 2 mo. Results of repeat CT scan were unchanged.

Patient 2

The patient was born at 36 wk to a 25-year-old gravida 3, para 2 white woman with micrognathia, microcephaly, and a mild mental retardation. The family history was otherwise unremarkable. Vaginal delivery followed third trimester polyhydramnios and prolonged rupture of membranes, yielding a severely depressed (Apgars 0 and 1) male infant weighing 2,000 gm. Neonatally the infant had hyaline membrane disease, hyperbilirubinemia, and seizures. At 10 wk, the OFC was 35 cm, length 54 cm, and weight 4,100 gm. There was a right anophthalmia, left cleft lip and cleft palate, bilateral malformed ears, preauricular tags, and a nasal tag (Fig. 1C,D). The external auditory meatus was small on the left, absent on the right. Additional malformations were left choanal atresia and micrognathia. Roentgenograms showed asymmetric calvaria, hypoplastic left mandibular ramus, and intracranial calcification in the occipital region. CT scan (Fig. 2B) showed dilated ventricles, hypoplastic septum pellucidum, partially calcified, and partially fatty lesion in the left posterior hemisphere. The dilated ventricles ascribed to midline hypoplasia of the brain have not enlarged further. EEG was consistent with diffuse neuronal disturbance and underlying seizure tendency. Ophthalmology evaluation showed no eye tissue OD and microphthalmia OS. A mild hearing loss was demonstrated. The patient tolerated repair of the cleft lip and is now growing along the 10th centile at 18 mo with a developmental age of about 10 mo.

Patient 3

The patient was born at 41 wk to a 17-year-old gravida 2, para 1 white woman. The family history was unremarkable. The gestation was complicated by polyhydramnios, and the infant required resuscitation. Birth weight was 3.22 kg. On examination at 2 days the infant was found to have plagiocephaly, left hemifacial microsomia, OFC of 34.5 cm, a medial coloboma of the upper lid and a lipoepidermoid cyst in the lower outer quadrant OS, a small right ear, lobular remnant of left ear with preauricular tags, a left cleft lip and cleft palate, severe micrognathia, bifid right thumb, left simian crease, Tetralogy of Fallot, left mandibular and maxillary hypoplasia on skull films, hemivertebrae at T3-4, hearing loss, and normal chromosomes. The infant had recurrent aspiration pneumonia, chronic atelectasis and gastroesophageal reflux managed by tracheostomy, and Nissen fundoplication. He also had a Blalock-Taussig shunt. Repair of the cleft lip and palate was not successful. At 2 yr the patient had a physical size and developmental level appropriate for 6 mo. He died at 3 yr of pneumonia. No autopsy was obtained.

Patient 4

The patient was born at term to a 31-year-old gravida 3, para 1, abortus 1 oriental mother who had severe nausea and vomiting during her pregnancy. Doxylamine succinate was taken throughout the pregnancy. Delivery and family history were unremarkable. Birthweight was 2.9 kg. Neonatally, the infant had hyperbilirubinemia,

feeding problems, reflux vomiting, dehydration, lethargy, weight loss, and Escherichia coli septicemia. At 6 wk he weighed 2.78 kg, with disproportionate microcephaly, a small anterior fontanel with overlapping sutures, abnormal posturing, hyperreflexia, prominent lateral ventricles, slight deficiency of frontal lobe white matter, a prominent pontine cistern on CT scan, and severe disorganization of EEG pattern. Brain stem auditory evoked responses showed normal cortical transmission by bone, but none by air. Congenital hip dislocation was treated by Pavlik harness.

At 6 mo he had a weight of 5.8 kg, length of 66.5 cm, and OFC of 40 cm. The head was asymmetric and brachycephalic with hypoplasia and indentation of the buccinator and parotid regions. The ears were small and posteriorly angulated with simple conchae and malformed helices. There was micrognathia and a cleft of the posterior soft palate. Other anomalies included right simian crease, a hemangioma on the dorsum of the left hand, a deep pilonidal sinus, a left horseshoe kidney with duplication of collecting system, and a "butterfly" vertebra at T5. The hearing loss was confirmed and treated with hearing aid. Gastroesophageal reflux was demonstrated and corrected surgically. At 18 mo has a developmental age of about 10 mo.

RESULTS

Table I summarizes the manifestations of our cases and compares them with those of other previously reported Goldenhar syndrome (GS) cases with cranial defects. The intracranial dermoid cysts in patients 1 and 2 were the most unusual findings. On skull films these masses contained calcium that surrounded a fatty center demonstrated on CT scans (Fig. 2). This appearance was similar to that of the dermoid tumor demonstrated in a 28-year-old woman with GS by Murphy et al [1980]. When the latter tumor was removed, it was shown to contain the stratified squamous epithelium and sebaceous gland typical of dermoid cysts.

Patients 1–4 were striking for the number and severity of their anomalies compared to most other cases of GS. All four had severe first and second branchial arch anomalies with cleft lip and palate, while patients 1, 3, and 4 had radial or vertebral malformations. Patients 1 and 4 had dextrocardia, patient 3 had Tetralogy of Fallot. These cardiac anomalies are characteristic of patients with GS [Greenwood et al, 1974]. Cases 1 and 2 had intrauterine growth retardation, and all four had severe failure to thrive presumably owing to swallowing and feeding difficulties.

Skull defects in previously reported GS patients include cranial asymmetry, hypoplasia of the petrous bone or ethmoid bones, platybasia, and absence of the internal auditory canal (Table I). Brain anomalies include hydrocephalus, Arnold-Chiari malformation, unilateral arhinencephaly, and encephalocele. The occurrence of the latter anomaly in 2 patients in Table I and 11 cases reported or cited by Cohen [1971] establishes encephalocele as a rare component of GS.

Striking findings in GS patients selected for cranial defects include male sex preponderance (12/16), growth failure (5/5), facial asymmetry (11/13), eye defects (15/16), hearing deficit (8/8), visceral defects (7/15), and vertebral anomalies (11/16). Better documentation and reporting of these anomalies in severely affected GS patients will increase their usefulness as indicators of intellectual potential. The incidence of mental retardation in GS patients with cranial defects was 9/11 (82%, Table I). A series of GS patients selected by other criteria had a 25% [Feingold and

TABLE I. Manifestations of Patients With Goldenhar Syndrome and Cranial Defects

Manifestations	Present cases				Cohen 1971				Shokeir [1977]	Kirkham [1971]
Sex-original	1	2	3	4	5	6	7	8	9	10
case number	F	M	M	M	M-1	M-2	M-3	M-4	M-1	M
Growth										
Intrauterine growth retardation	+[a]	+	−	−	?	−	?	?	?	−
Failure to thrive	+	+	+	+	?	?	?	?	?	?
Orofacial										
Facial asymmetry	+	+	+	−	+	+	+	+	?	?
Anopthalmia/ microphthalmia	−	+	−	−	+	+	+	+	+	−
Optic coloboma	+	−	+	−	−	−	−	−	+	+
Optic dermoid/ lipodermoid cyst	+	−	+	−	−	−	−	−	+	−
Malformed ears	+	+	+	+	+	+	+	+	+	+
Hearing deficit	+	+	+	+	?	?	?	?	+	+
Cleft lip/cleft palate	+	+	+	+	+	+	+	−	+	−
Micrognathia	+	+	+	+	−	−	+	−	−	?
Organs										
Cardiac defect	+	−	+	+	−	−	−	−	+	−
Renal anomaly	?	−	−	+	?	?	?	?	?	−
Pulmonary hypoplasia	−	−	+	−	−	−	−	−	−	−
Skeletal										
Radial defect	+	−	+	−	−	−	−	−	−	−
Vertebral defect	+	−	+	+	+	−	−	−	+	+
Cranial										
Mental retardation	+	+	+	+	+	+	+	+	?	?
Microcephaly	+	+	−	+	?	?	?	?	?	?
Cranial asymmetry	+	+	+	+	+	+	+	+	?	?
Intracranial dermoid	+	+	−	−	−	−	−	−	?	?
Encephalocele	−	−	−	−	−	−	−	−	+	−
Hydrocephalus	−	+	−	+	−	−	−	−	?	?
Skull defect	−	+[b]	−	−	−	−	+[c]	−	+	+[d]
Miscellaneous	+[g]	+[h]	−	+[i]	−	−	−	−	−	+[j]

[a]Manifestation present (+), manifestation not excluded (?), or manifestation absent (−) by author's interpretation.
[b]Choanal atresia.
[c]Parietal osseous defect.
[d]Petrous bone hypoplasia, absent internal auditory canal.
[e]Platybasia.
[f]Ethmoid hypoplasia
[g]Cerebellar hypoplasia.
[h]Hypoplastic septum pellucidum, abnormal EEG.
[i]Frontal lobe dysplasia, abnormal EEG.
[j]Calcified anterior falx cerebri.
[k]Arnold-Chiari malformation.
[l]Unilateral arhinencephaly.
[m]Occipital scalp defect.

Gupta et al [1968] 11 M	Michaud and Sheridan [1974] 12 F	Lambda and Ramamurthy [1973] 13 M-2	Murphy et al [1980] 14 F	Aleksic et al [1975] 15 F	Smithells [1964] 16 M	Incidence (percent) 12M 4F
?	?	?	?	?	+	3/ 7 (43)
?	+	?	?	?	?	5/ 5 (100)
+	−	+	+	+	?	11/13 (85)
−	−	+	−	+	?	8/15 (53)
−	+	−	+	?	−	6/15 (40)
+	+	+	+	?	+	8/15 (53)
+	+	+	+	+	+	16/16 (100)
?	?	+	+	?	?	8/ 8 (100)
−	−	−	−	+	−	9/16 (56)
?	?	?	?	+	+	7/11 (64)
?	−	?	−	+	+	6/14 (43)
?	−	?	−	−	−	1/ 8 (13)
−	−	?	−	−	−	1/15 (6.7)
−	−	−	−	−	−	2/16 (13)
−	+	+	+	+	+	11/16 (69)
?	−	+	−	?	?	9/11 (82)
−	−	?	−	?	?	3/ 7 (43)
+	−	+	−	+	?	11/13 (85)
?	?	?	+	−	?	3/10 (30)
+	−	−	−	−	−	2/16 (13)
+	+	?	+	−	?	5/12 (42)
+	+[e]	−	−	+[f]	?	7/15 (47)
−	+[k]	−	−	+[l]	+[m]	7/16 (44)

Baum, 1978], 16.7% [Shokeir, 1977], or 6% [Hollowich and Verbeck, 1969] incidence of mental retardation. Clearly these are low estimates since many patients die or are lost to follow-up before intellectual function can be adequately assessed. Table I demonstrates that GS patients with multiple, severe, or unusual malformations face a higher risk for retardation than the 10–15% quoted in textbooks [Gorlin et al, 1976].

DISCUSSION

This report and review of patients with GS and cranial defects emphasizes the broad spectrum of anomalies that can be anticipated. Table I includes defects of heart, lung, kidney, radial ray, and the brain in addition to malformations of eye, spine and branchial arch derivatives. Cohen's [1971] recommendation of skeletal survey in severely affected patients is further supported since the neurologic anomalies–microcephaly, cranial asymmetry, skull defects, hydrocephalus, and certain intracranial

masses — may be documented or suspected on skull films. Abnomalities of cranial volume, shape, or calcification should then be defined by CT scan. Defects of the external or internal auditory canal demand early audiologic evaluation. The vigorous cardiorespiratory support and plastic surgery which GS patients often require should be undertaken only after parents and physicians appreciate the spectrum of defects and realistically appraise the patient's intellectual potential.

Cohen [1971], Michaud et al [1974], and Murphy et al [1980] have emphasized neurologic abnormalities in their patients. Cherstvoy et al [1978] also report four cases of GS with brain anomalies ("dysplasia" of the frontal lobe, internal capsule, lissencephaly) and normal chromosomes, but their patients were not described in sufficent detail for inclusion in this report. Table I is a first step towards a defined set of neurologic defects and developmental indicators in GS patients.

As described in patients with anterior encephalocele [Rapport et al, 1981], the cranial defects in GS represent a developmental disturbance of neuroectoderm (anophthalmia, frontal lobe hypoplasia, dermoid cysts) and cranial mesoderm (skull defects). The optic primordium and anterior neuropore are both present in the 24-day human embryo and their subsequent development is central to the development of facial structure [Rapport et al, 1981]. These cranial anomalies fit in with other GS defects in defining a similar period of dysmorphogenetic action. Formation of the branchial arches (malformed ears, micrognathia), ureteral bud (renal abnormalities), sclerotomes (vertebral malformations), limb buds (radial aplasia), and cardiac rotation (dextrocardia, transposition) also begin at 23–30 days of gestation [Pauli et al, 1981; Quan and Smith, 1973]. The similar embryologic timing of GS anomalies, like those found in the VATER association [Quan and Smith, 1973], suggests that the respective Anlagen share characteristics of cell biology, vascular supply, or topology during the critical period of injury. Thorough delineation of GS defects will increase our understanding of these relationships.

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