Oculoauriculovertebral Spectrum: An Updated Critique

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A comprehensive review and critical analysis of oculoauriculovertebral spectrum are provided. Topics discussed include nosologic problems, epidemiology, etiology (chromosomal, monogenic, teratogenic), and pathogenesis (hematoma formation, other vascular mechanisms, overripeness ovopathy). Clinical manifestations are thoroughly reviewed, updated, and documented for craniofacial features, central nervous system characteristics (including the wide spectrum of CNS malformations that make up the so-called "expanded Goldenhar complex"), congenital heart defects, and various other anomalies (kidney, lung, gastrointestinal tract). A number of conditions are discussed that are commonly differentiated from oculoauriculovertebral spectrum but have overlapping relationships, in some instances, with frontonasal dysplasia, branchio-oto-renal (BOR) syndrome, Townes-Brocks syndrome, Wildervanck syndrome, DiGeorge sequence, and several associations (VATER, CHARGE, and MURCS).

KEY WORDS: *oculoauriculovertebral dysplasia, Goldenhar syndrome, hemifacial microsomia, branchial arch syndrome*

In the 1960s hemifacial microsomia and Goldenhar syndrome (or oculoauriculovertebral dysplasia) were defined in a straightforward fashion. Hemifacial microsomia was a condition affecting primarily aural, oral, and mandibular development. The disorder varied from mild to severe, and facial involvement was limited to one side in many cases, although bilateral involvement was also known to occur with more severe expression on one side. Goldenhar syndrome, which was characterized additionally by vertebral anomalies and epibulbar dermoids, was considered a variant of this complex. By 1976, so much overlap between hemifacial microsomia and oculoauriculovertebral dysplasia had been reported that no valid distinction could be made. In *Syndromes of the Head and Neck,* we said:

> The etiology is unresolved and probably complicated. On the one hand, we have seen many transitional forms between hemifacial microsomia and the Goldenhar syndrome, suggesting a continuous spectrum. . . . On the other hand, the great variability observed in sporadic cases and the fact that familial instances occur, which seem to have different modes of inheritance, suggest etiologic heterogeneity. (Gorlin et al, 1976)

Thus, not only could nosologic splitting be invalid, but "lumping" might be inappropriate, as well.

The process of syndrome delineation, which has been discussed extensively elsewhere (Cohen, 1982), often demonstrates the clear separation of etiologic entities with time. However, even as the phenotypic spectrum of oculoauriculovertebral dysplasia has expanded with time, the result has been greater confusion, not clarification. The situation may be summed up best by the "Murphyism", "Just because your doctor knows the name of your condition doesn't mean he knows what it is."

NOSOLOGIC PROBLEMS

The disagreements about oculoauriculovertebral spectrum reflect the frustrations that geneticists, syndromologists, and dysmorphologists have encountered and continue to encounter in grappling with interpretation. M.M. Cohen Jr., and R.J. Gorlin think of oculoauriculovertebral spectrum as being both etiologically and pathogenetically heterogeneous with an extraordinarily wide range of phenotypic expression. D.E. Poswillo of London, England, (personal communication, 1987) believes that hemifacial microsomia and Goldenhar syndrome are separate conditions and do not reflect a continuum or spectrum. J.M. Opitz of Helena, Montana, (personal communication, 1987) holds the opinion that neither the term dysplasia (i.e., oculoauriculovertebral dysplasia) nor syndrome fits the condition. He thinks that the oculoauriculovertebral phenotype is a causally heterogeneous developmental field defect. B.D. Hall of Lexington, Kentucky, (personal communication, 1987) believes that because heterogeneous conditions representing so many different ascertainment biases have been described, naming this group is a useless and mislead-

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ing exercise. Finally, the many terms used for this complex (Table 1) emphasize nosologic problems (Fig. 1) and indicate the wide spectrum of anomalies described and emphasized by various authors.

There are numerous reviews of the subject (François and Haustrate, 1954; Grabb, 1965; Stark and Saunders, 1967; Berkman and Feingold, 1968; Hollwich and Verbeck, 1969; Cohen, 1971 and 1982; Baum and Feingold, 1973; Converse et al, 1973; Mounoud et al, 1975; Ross, 1975; Shokeir, 1977; Kaye et al, 1979; Melnick, 1980; Figueroa and Pruzansky, 1982; Burck, 1983; Rollnick and Kaye, 1983; Tenconi and Hall, 1983; Aleksic et al, 1984; Mansour et al, 1985; Rollnick et al, 1987; Rollnick, 1988). Although there are no agreed upon minimal diagnostic criteria, the facial phenotype is characteristic when enough manifestations are present. In some instances, isolated microtia or auricular or preauricular abnormality may represent the mildest manifestation (Grabb, 1965; Gorlin et al, 1976; Melnick and Myrianthopoulos, 1979; Rollnick and Kaye, 1983; Tenconi and Hall, 1983; Bennun et al, 1985). Unilateral microtia or ear abnormality (including preauricular tags) has been suggested as a mandatory feature by some authors (Rollnick and Kaye, 1983). Involvement is not limited to facial structures. Cardiac and skeletal anomalies are common, and other anomalies may also occur. In particular, the so-called "expanded Goldenhar complex" has demonstrated a wide spectrum of central nervous system malformations not previously appreciated (Aleksic et al, 1975, 1976, 1983, and 1984; Pauli et al, 1983; Wilson, 1983). It has been suggested by several authors that invalid nosologic splitting, on the one hand, and inappropriate lumping, on the other, complicate our understanding of this complex (Herrmann and Opitz, 1969; Opitz and Faith, 1969; Pashayan et al, 1970; Cohen, 1971 and 1982; Gorlin et al, 1976; Tenconi and Hall, 1983). The Goldenhar variant of the spectrum may constitute only about 10 percent of the cases (Rollnick and Kaye, 1983).

EPIDEMIOLOGY

Poswillo (1974) suggested a frequency of oculoauriculovertebral spectrum of one per 3,500 births, although he presented no data to support this conjecture. Grabb (1965) estimated one case per 5,600 births, a frequency in accord with our own (R.J. Gorlin and M.M. Cohen, Jr., personal observation). Stoll et al (1984) noted a prevalence of one per 19,500 consecutive births. Melnick (1980) recorded a frequency of one per 26,550 live births in a prospective newborn study. The male:female ratio is at least 3:2 (Gorlin et al, 1976; Smith, 1982; Wilson, 1983; Rollnick et al, 1987). There is also a 3:2 ratio of right-sided versus left-sided involvement (Rollnick et al, 1987).

TABLE 1 The Varied Nomenclature Applied to Oculoauriculovertebral Spectrum

Name	*Authors*
Hemifacial microsomia	Gorlin and Pindborg, 1964
Oculoauriculovertebral dysplasia	Gorlin et al, 1963
Goldenhar syndrome	Sugar, 1966
Goldenhar-Gorlin syndrome	Aleksic et al, 1975
First arch syndrome	McKenzie, 1958
First and second branchial arch syndrome	Grabb, 1965
Lateral facial dysplasia	Ross, 1975
Familial facial dysplasia	Ide et al, 1970
Unilateral craniofacial microsomia	Grayson et al, 1983
Otomandibular disostosis	Francois and Haustrate, 1954
Oral-mandibular-auricular syndrome	Stark and Saunders, 1967
Unilateral mandibulofacial dystosis	Wilson, 1958
Unilateral intrauterine facial necrosis	Walker, 1961
Auriculo-branchiogenic dysplasia	Caronni, 1967
Facio-auriculo-vertebral malformation spectrum	Smith, 1982
Oculoauriculovertebral spectrum	Present paper

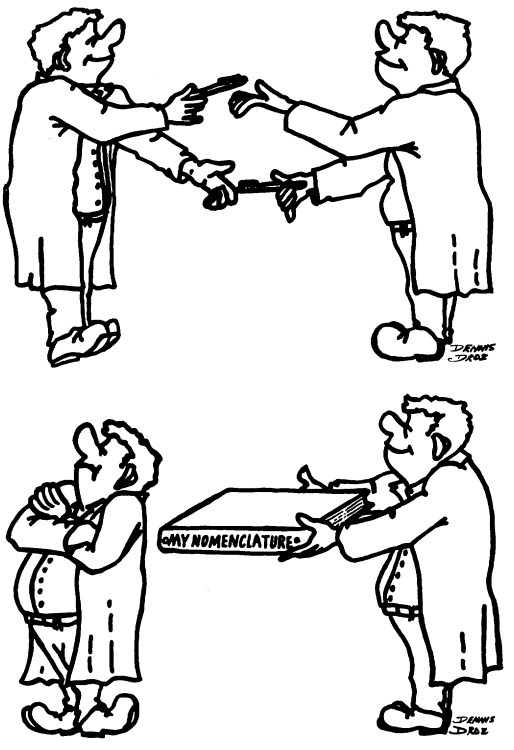

FIGURE 1 *A*, **Academicians are more likely to share each other's toothbrush . . .** *B*, **than each other's nomenclature. From Cohen MM Jr. (1982).**

ETIOLOGY

Oculoauriculovertebral spectrum has obvious etiologic heterogeneity. A number of chromosomal anomalies have been associated including del(5p) (Dyggve and Mikkelsen, 1965; Ladekarl, 1968; Neu et al, 1982), del(6q) (Greenberg et al, 1987), trisomy 7 mosaicism (Hodes et al, 1981), dup(7q) (Hoo et al, 1982), del(8q) (Townes and White, 1978), trisomy 9 mosaicism (Wilson and Barr, 1983), trisomy 18 (Bersu and Ramirez-Castro, 1977; Greenberg et al, 1987), trisomy 18 mosaicism (Clarren and Salk, 1983), recombinant chromosome 18 (Sujansky and Smith, 1981), del(18q) (Curran et al, 1970), ring 21 chromosome (Greenberg et al, 1987), del(22q) (Greenberg et al, 1987; Herman et al, 1988), 49,XXXXY (Kushnick and Colondrillo, 1975), 47,XXY (Poonawalla et al, 1980), 47,XXX (Aouchiche and Boyer Nouar, 1972), and 49,XXXXX (Schroeter et al, 1980). Some of these associations are meaningful and

some occur coincidently. Meaningful chromosomal defects are likely to be those karyotypes observed repeatedly. Therefore del(5q), trisomy 18, and perhaps dup(7q) may be significant associations. X chromosome aneuploidy states noted in several instances have been of different types and may or may not be significant.

Several teratogenic agents have produced oculoauriculovertebral spectrum in humans. The phenotype has been observed in infants of diabetic mothers (Grix, 1982; Johnson and Fineman, 1982; Israel et al, 1987) and in infants born to pregnant women exposed to thalidomide (Miehlke and Partsch, 1963; Livingston, 1965; Rosendal, 1965), primidone (Gustavson and Chen, 1985), and retinoic acid (Lammer et al, 1985).

Discordance in monozygotic twins has been reported frequently (Bock, 1961; Cordier et al, 1970; Papp et al, 1974; Setzer et al, 1981; Ebbesen and Petersen, 1982; Burck, 1983; Rollnick and Kaye, 1983; Connor and Fernandez, 1984; Gómez-García et al, 1984; Perez Alvarez et al, 1984; Stoll et al, 1984; Boles et al, 1987). Less commonly, concordance with variable expression has been documented in monozygotic twins (Ter Haar, 1972; Rollnick, 1988; Ryan et al, 1988). Discordance has been reported in dizygotic twins (Grabb, 1965; Heimann, 1968; Rapin and Ruben, 1976; Shprintzen, 1982; Connor and Fernandez, 1984), in twins of undetermined zygosity (Goldenhar, 1952; Berthelon and Cremer, 1969), and in triplets (Yovich et al, 1985). The interested reader is referred to the excellent analysis of Burck (1983).

Most cases of oculoauriculovertebral spectrum are sporadic, but familial instances have been reported. Affected individuals in successive generations have been observed repeatedly (Grabb, 1965; Herrmann and Opitz, 1969; Summitt, 1969; Cohen, 1971 and 1982; Thomas, 1980; Setzer et al, 1981; Regenbogen et al, 1982; Rollnick and Kaye, 1983 and 1985; Taysi et al, 1983). The affected mother and daughter with radial limb defects noted by Moeschler and Clarren (1982) may represent trisomy 18 mosaicism (Clarren and Salk, 1983). Within single families, expression has varied from complete hemifacial microsomia in several affected individuals, to mild hemifacial microsomia in some relatives, and to simple preauricular tags or a mildly dysplastic ear in others (Cohen, 1982; Rollnick and Kaye, 1983) (Figs. 2–4). A number of reports support the notion that an isolated dysplastic ear or preauricular tag may represent the mildest expression of the disorder in some families (Grabb, 1965; Gorlin et al, 1976; Melnick and Myrianthopoulos, 1979; Rollnick and Kaye, 1983; Tenconi and Hall, 1983; Rollnick et al, 1987). Vertical transmission of the Goldenhar variant in some family members with lack of ocular involvement in others has been observed (Summitt, 1969; Regenbogen et al, 1982).

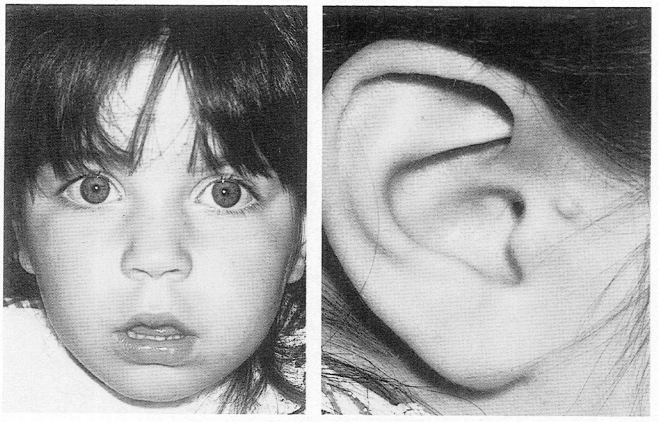

FIGURE 3 Sister of patient shown in Figure 2. Note preauricular tag, which represents an accessory auricular hillock. From Cohen MM Jr. (1982).

Affected siblings with normal parents have also been reported (Grabb, 1965; Saraux et al, 1963; Saraux and Besnainou, 1965; Kirke, 1970; Krause, 1970). Consanguinity has been noted in a single sporadic instance (Pashayan et al, 1970). Autosomal dominant and autosomal recessive inheritance have both been hypothesized to explain various familial occurrences. Etiologic heterogeneity is likely. Overall, the empiric recurrence risk is low, being about 2 to 3 percent (Grabb, 1965; Rollnick and Kaye, 1983).

Pathogenesis

Poswillo (1973, 1974, 1975) reported a phenocopy of hemifacial microsomia in mice following maternal adminis-

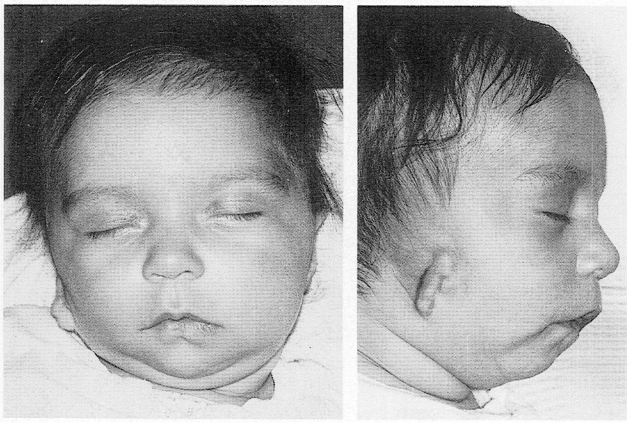

FIGURE 2 Hemifacial microsomia. From Cohen MM Jr. (1982).

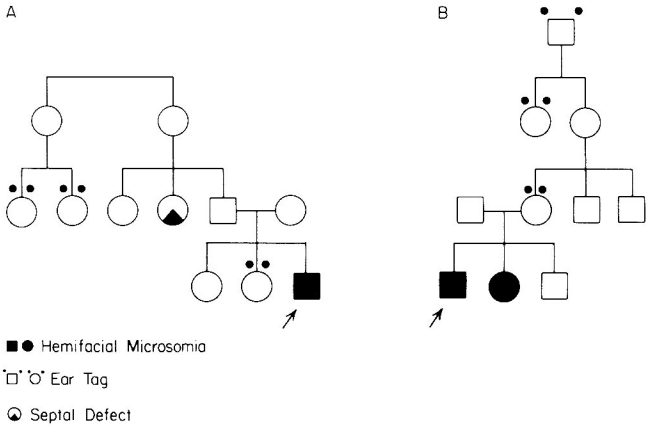

FIGURE 4 Pedigrees with hemifacial microsomia in which minimally affected relatives have only preauricular tags. Pedigree A of proband and sister shown in Figures 2 and 3. From Cohen MM Jr. (1982).

tration of triazene and in monkeys following maternal ingestion of thalidomide. He proposed that pathogenesis was based on embryonic hematoma formation arising from the anastomosis that precedes formation of the stapedial artery stem. Variation in the severity of hemifacial microsomia was found to depend on the size and extent of hematoma formation, with large hematomas interfering more severely with branchial arch growth by taking longer to resolve than small hematomas.

Some cases of the amniotic band spectrum of disruptions have been noted to simulate hemifacial microsomia (Hall, 1979). In such instances, hemifacial microsomia may be caused by intrauterine compression secondary to oligohydramnios. Kennedy and Persaud (1977) extracted amniotic fluid from pregnant rats at 16 days' gestation and studied the embryos at various times thereafter. On histologic examination, they found hemorrhage and edema, followed by tissue necrosis in the cartilage and mesenchymal preskeleton of the developing limbs. The observed reduction defects and amputations of the limbs resulted from the venous stasis, hypervolemia, and embryonic oxygen deficiency caused by intrauterine compression. Kennedy and Persaud (1977) did not give a detailed histologic evaluation of the branchial arch region, but they did note that micrognathia was observed in addition to subcutaneous hemorrhages in the head region. Thus, intrauterine compression might be construed as a possible mechanism for producing hematoma formation in the branchial arch region, thereby resulting in hemifacial microsomia. Because hemifacial microsomia in humans may occur with limb reduction defects in some cases (Gorlin et al, 1976), the association may be compatible with Poswillo's hypothesis. If hemifacial microsomia were to be observed with amniotic band–related limb abnormalities, this would also be compatible with Poswillo's hypothesis.

As previously indicated, hemifacial microsomia is both etiologically and pathogenetically heterogeneous. Hematoma formation itself has heterogeneous causes including hypoxia, hypertension, pressor agents, salicylates, and anticoagulants (Poswillo, 1973). It is also important to recognize that, although embryonic hematoma formation may explain some cases of hemifacial microsomia, it doesn't explain all cases. For example, in some familial instances, affected relatives may have only preauricular tags (see Figs. 2–4). It is difficult to conceive of any basic mechanism causing hematoma formation that would explain these cases. In minimally affected individuals, the ear and mandible are well formed, and the preauricular tag seems to represent an accessory auricular hillock, an example of embryonic redundant morphogenesis. To postulate separate pathogenetic mechanisms to explain instances of hemifacial microsomia and accessory ear tags in the same family seems unnecessarily complicated. The most parsimonious hypothesis should take into account that the two pedigrees in Figure 4 represent a single entity that is variably expressed and genetically transmitted. Another example that shows the

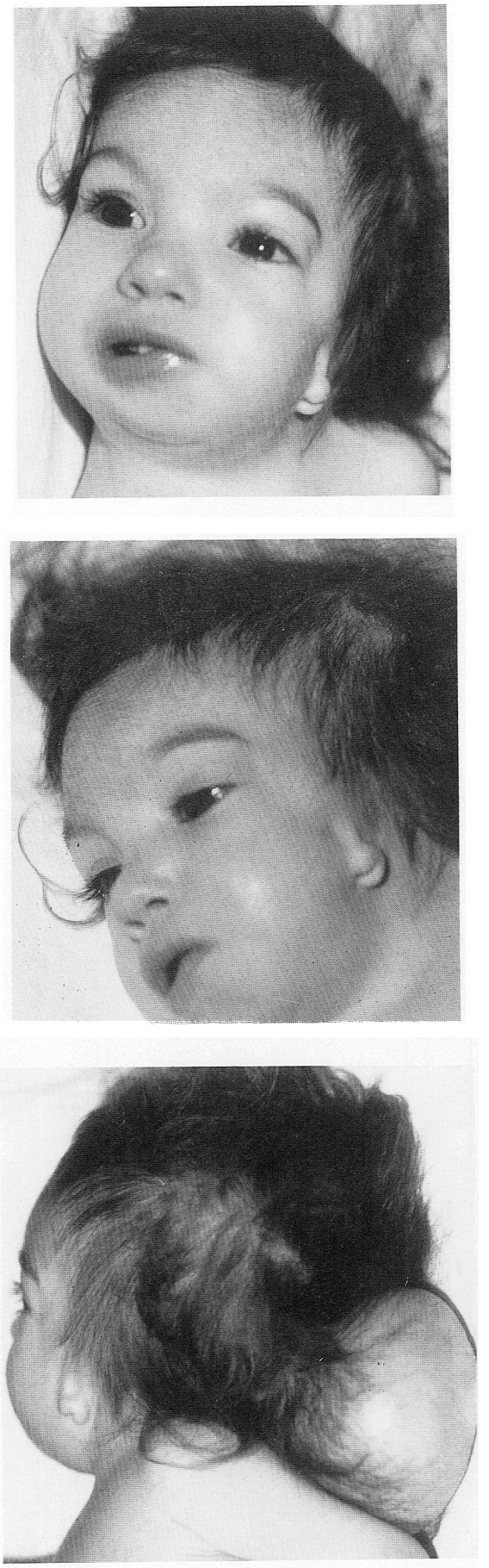

FIGURE 5 Patient with true malformation syndrome in which hemifacial microsomia is one component. Note hemifacial microsomia and occipital encephalocele. See also Figures 6 and 7. From Cohen MM Jr. (1982).

limitations of the hematoma hypothesis is a true malformation syndrome in which hemifacial microsomia is only one component. The patient shown in Figures 5 through 7 has hemifacial microsomia, occipital encephalocele, hypoplastic lung, vertebral anomalies, and renal agenesis. These anomalies most likely have a common cause (although unknown) rather than being caused by different factors acting independently. Whatever mechanism is responsible for one malformation should be responsible for the others. To date, there is no experimental evidence that hematoma formation can cause encephaloceles or renal agenesis. Therefore, it seems unlikely that hematoma formation has anything to do with the pathogenesis of this recurrent pattern syndrome (Cohen, 1982).

Other clinical reports have suggested the possibility of vascular pathogenesis. Gorlin et al (1963) noted that abnormal vascular supply to cephalic neural crest cells could impede embryonic development in the branchial arches. Robinson et al (1987) reported evidence of carotid artery occlusion in two cases. Moore et al (1987) demonstrated absence of the internal carotid artery in a severe case with hemifacial defects and unilateral hydranencephaly. In such cases it is not always clear whether vascular accidents or simply inadequate vascular supply is primary or whether craniofacial hypoplasia is primary, thereby resulting in diminished caliber of the vessels. Soltan and Holmes (1986) proposed a hypothesis that links genetic causes and vascular disruption. For five relatives with different malformations usually attributed to vascular accidents (including one possible variant of oculoauriculovertebral spectrum), they suggested an underlying familial vascular anomaly predisposing to vascular accidents and resulting in various malformation complexes.

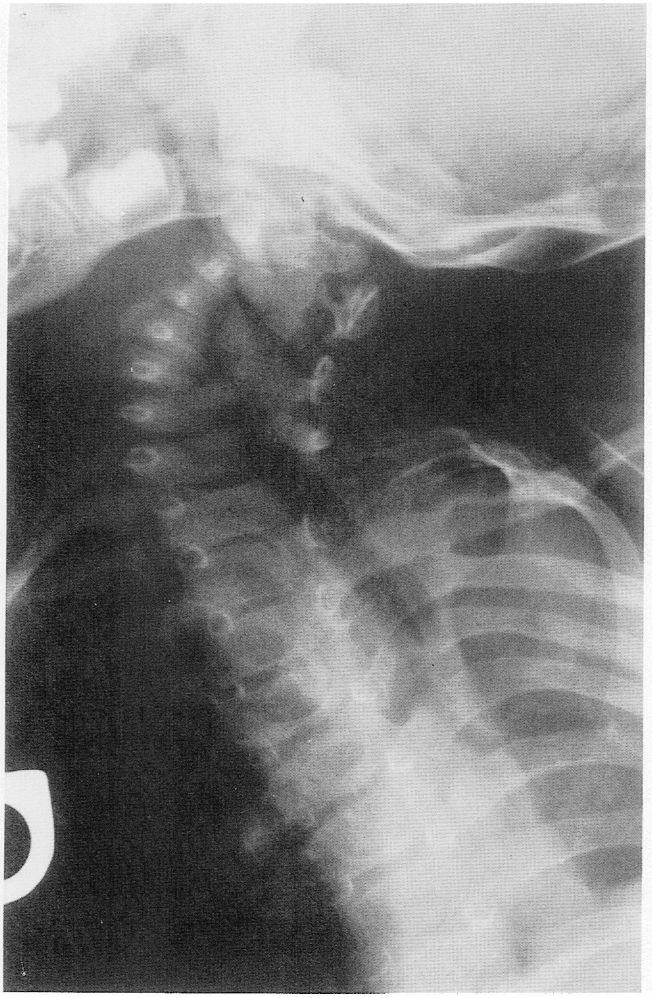

FIGURE 6 Patient with true malformation syndrome in which hemifacial microsomia is one component. Note hypoplastic left lung and vertebral anomalies. See also Figures 5 and 7. From Cohen MM Jr. (1982).

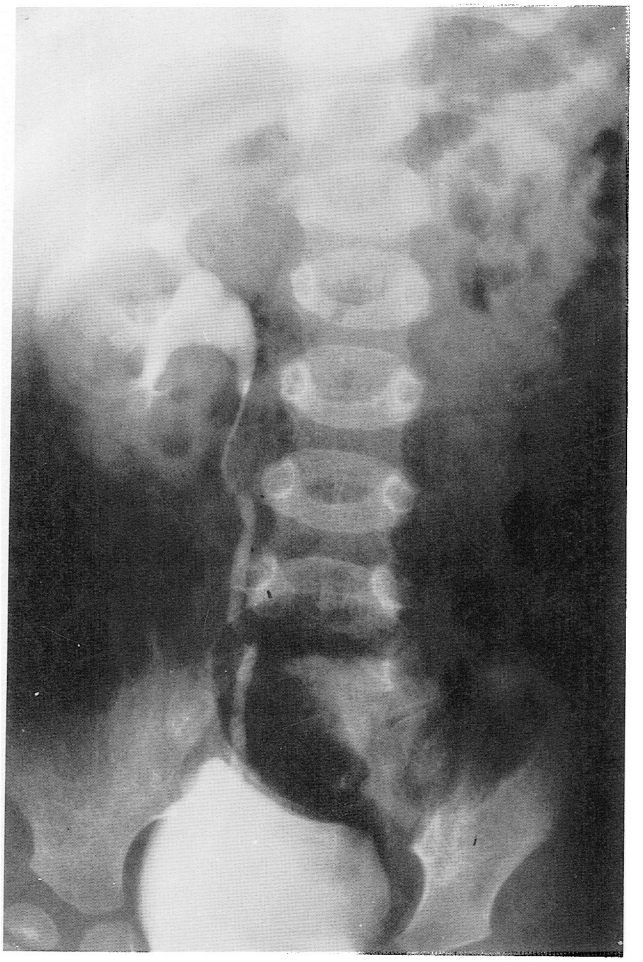

FIGURE 7 Patient with true malformation syndrome in which hemifacial microsomia is one component. Note unilateral renal agenesis. See also Figures 5 and 6. From Cohen MM Jr. (1982).

Various retinoic acid derivatives have been studied for their pathogenetic role in the production of branchial arch anomalies. Using vitamin A palmitate as a teratogen in pregnant rats, Poswillo (1974) produced a Treacher Collins–like condition in the newborn rat pups resulting from early destruction of neural crest cells, which normally migrate into the branchial arches during early embryonic life. Sulik et al (1987, 1989), using 13-*cis* retinoic acid as a teratogen in pregnant mice, also produced a phenotype similar to Treacher Collins syndrome in mouse pups. The effects on first and second branchial arch ectodermal placodal cells following the release of neural crest cells from the neural folds into the developing cranial region were of major significance in the pathogenesis of the anomalies en-

countered. The fact that retinoic acid derivatives can affect not only the branchial arch region, but also the cardiovascular system, the axial skeleton, and the central nervous system (Lammer et al, 1985; Sulik et al, 1987 and 1989) suggests that these teratogens should be studied further to determine whether an oculoauriculovertebral spectrum animal model can be produced.

Overripeness ovopathy as a possible cause of oculoauriculovertebral spectrum has been suggested (Jongbloet, 1987; Yovich et al, 1987). The theory has been offered in an attempt to explain sporadic (as distinct from familial) occurrence, both concordance and discordance in monozygotic twins, accompanying chromosomal anomalies, and the wide spectrum of associated central nervous system, cardiac, renal, and skeletal malformations. However, this theory subsumes too much heterogeneity under a single principle. Overripeness ovopathy, although introduced 20 years ago as an explanation for Goldenhar syndrome (Jongbloet, 1968), has not received serious consideration in major reviews of oculoauriculovertebral spectrum. The interested reader can find a recent review by the major proponent of the theory (Jongbloet, 1987).

CLINICAL MANIFESTATIONS

Extreme variability of expression is characteristic. About 50 percent of patients have been observed to have other anomalies in addition to the principal features of the defect (Rollnick et al, 1987). Some infants are small for gestational age and may have feeding difficulties secondary to an anatomically narrow pharyngeal airway or to a cleft lip with or without cleft palate.

Craniofacial Features

Marked facial asymmetry is present in 20 percent of cases, but some degree of asymmetry is evident in 65 percent. The asymmetry may not be apparent in the infant or young child, but it becomes evident with growth, usually by 4 years of age. Adequate overlying soft tissue may mask the skeletal asymmetry. Conversely, deficient soft tissue overlying adequate bony structures may result in facial asymmetry (Figueroa and Pruzansky, 1982).

The maxillary, temporal, and malar bones on the more severely involved side are somewhat reduced in size and flattened (Rune et al, 1981). Asymmetry may result from aplasia or hypoplasia of the mandibular ramus and condyle. Some patients manifest mild pneumatization of the mastoid region. About 10 to 33 percent of patients have bilateral involvement (Grabb, 1965; Burck, 1983; Rollnick et al, 1987), but one side is nearly always more severely involved than the other. Among 193 unilaterally affected patients studied by Rollnick et al (1987), the right side was involved in over 60 percent. Frontal bossing can be noticeable at birth but becomes less apparent with age (Gorlin et al, 1963).

Blepharoptosis or narrowing of the palpebral fissure occurs on the affected side in about 10 percent of patients. Clinical anophthalmia or microphthalmia (Fig. 8) has been described in several patients (Cohen, 1971; Baum and Feingold, 1973; Aleksic et al, 1975; Shokeir, 1977; Wilson, 1983; Margolis et al, 1984). Epibulbar tumors are found in about 35 percent and are more frequently unilateral than bilateral (Goldenhar, 1952; Baum and Feingold, 1973; Mansour et al, 1985). They occur most often inferotemporally at the limbus. Their surface is usually smooth and frequently has fine hairs. They can occur at any location on the globe and may be dermoids, lipodermoids, or dermislike or mesoectodermal in nature. Lacrimal drainage abnormalities have been noted (Gupta et al, 1968; Baum and Feingold, 1973; Mansour et al, 1985). Unilateral colobomas of the upper eyelid are observed in about 20 percent of cases, usually unilaterally but sometimes bilaterally (Baum and Feingold, 1973). Other ocular motility disorders found

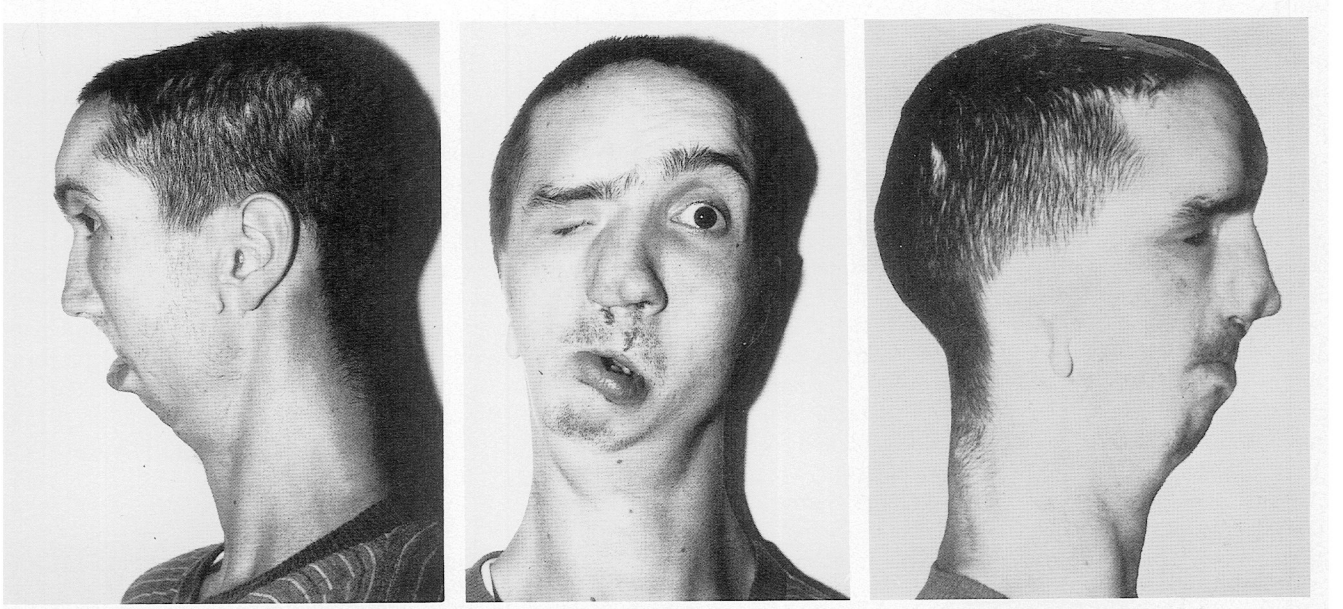

FIGURE 8 Marked facial asymmetry, unilateral (clinical) anophthalmia, absent right ear represented by large tag, left ear tag, micrognathia, and severe mental retardation. From Cohen MM JR. (1971). Variability versus "incidental findings" in the first and second branchial arch syndrome: unilateral variants with anophthalmia. Birth Defects Original Article Series 7(7):103–108.

in up to 25 percent include esotropia, exotropia, and Duane syndrome (Baum and Feingold, 1973; Aleksic et al, 1976; Miller, 1985). Choroidal or retinal colobomas, congenital cystic eye, and various other retinal abnormalities have been reported (Baum and Feingold, 1973; Margolis et al, 1984).

Malformation of the external ear may vary from anotia, to a hypoplastic mass of tissue that is displaced anteriorly and inferiorly, to a mildly dysmorphic ear (Figueroa and Pruzansky, 1982). Occasionally, both ears may be malformed. Preauricular tags of skin and cartilage are extremely common, and may be unilateral or bilateral. Supernumerary ear tags may occur anywhere from the tragus to the angle of the mouth. Preauricular sinuses may also be observed. Narrow external auditory canals are found in mild cases. Atretic canals are observed in more severe cases. Conductive and, less frequently, sensorineural hearing deficit has been reported. Causes include lesions of the middle and external ears, hypoplasia or agenesis of the ear ossicles, aberrant facial nerves, patulous eustachian tubes, and/or deformed skull base: conductive loss occurs with an overall frequency of 50 percent (Grabb, 1965; Converse et al, 1973; Ross, 1975; Gorlin et al, 1976).

At least 35 percent of the patients with agenesis of the mandibular ramus have associated macrostomia or lateral facial cleft, usually of mild degree (Gorlin et al, 1976). Involvement is nearly always unilateral and on the side of the more affected ear. Occasionally there is agenesis of the ipsilateral parotid gland, displaced salivary gland tissue, or salivary fistulae (Gorlin et al, 1976). The palatal and tongue muscles may be unilaterally hypoplastic, paralyzed, or both. Unilateral or bilateral cleft lip and/or cleft palate occurs in 7 to 15 percent of patients (Grabb, 1965; Rollnick et al, 1987). About 35 percent have velopharyngeal insufficiency (Luce et al, 1977). Shprintzen et al (1980) observed that the insufficiency resulted from asymmetry of movement of the lateral pharyngeal wall and palate.

Hypoplasia or absence of the ramus and condyle is observed. The degree of mandibular involvement has been graded by Figueroa and Pruzansky (1982). Malocclusion and canting of the occlusal plane are common, although the mandibular deformity has no effect on dental maturation on the affected side (Loevy and Shore, 1985).

Central Nervous System

A wide range of central nervous system defects may be associated, and reported frequencies of mental deficiency appear to have ascertainment bias. For example, series preselected for severe central nervous system malformations have a very high frequency of mental retardation, whereas those series reported as treated patients from various craniofacial centers tend to have a low frequency. Most estimates range from 5 to 15 percent (Hollwich and Verbeck, 1969; Shokeir, 1977). Higher frequencies of 37 and 82 percent are reported by Tenconi and Hall (1983) and Wilson (1983), respectively. Cohen (1971) suggested an association between micropthalmia, or clinical anopthalmia, and mental retardation because the eye is an outpouching of the primitive brain. However, patients with normal intelligence have also been noted.

Nearly all cranial nerves have been involved on occasion (Aleksic et al, 1984). Lower facial weakness has been reported to occur in about 10 percent of cases, possibly being related to bony involvement in the region of the facial canal (Grabb, 1965). Abnormal course of the seventh cranial nerve and unilateral aplasia of the trigeminal nuclei and the facial nerve (Ebbesen and Peterson, 1982; Aleksic et al, 1984) have been described, as has trigeminal anesthesia (Bowen et al, 1971; Ebbesen and Peterson, 1982). In our series of 281 patients, abnormalities of cranial nerves V and VII occurred in 17 percent (Kaye and Rollnick, 1989). Other cranial nerves involved have included I (Aleksic et al, 1975), II (Margolis et al, 1984), III, IV, VI (Aleksic et al, 1976), VIII, IX, X (Aleksic et al, 1984), and XII (Kaye and Rollnick, 1989).

For the expanded oculoauriculovertebral spectrum, brain malformations have been especially well discussed by Aleksic et al (1984). Anomalies may include microcephaly, occipital and frontal encephaloceles, hydrocephaly, lipoma, teratoma, dermoid cyst, Arnold-Chiari malformation, lissencephaly, arachnoid cyst, holoprosencephaly, unilateral arhinencephaly, and hypoplasia of the corpus callosum (Virchow, 1864; Hoffman-Egg and Velissaropoulos, 1953; Timm, 1960; Christiaems et al, 1966; Gupta et al, 1968; Herrmann and Opitz, 1969; Cohen, 1971; Michaud and Sheridan, 1974; Aleksic et al, 1975, 1983, and 1984; Gorlin et al, 1976; Shokeir, 1977; Murphy et al, 1980; Pauli et al, 1983; Wilson, 1983; Gustavson and Chen, 1985; Saller et al, 1988).

When flattened frontal encephalocele occurs, the patient appears to have frontonasal dysplasia together with ear tags, other ear anomalies, and even epibulbar dermoids (Fig. 9) (Gupta et al, 1968; Fleischer-Peters, 1969; Tenconi and Hall, 1983; Musarella and Young, 1986). Because encephalocele occurs more commonly in the occipital region than in the frontal region, we suggest that the cases of frontonasal dysplasia with epibulbar dermoids and ear tags simply represent oculoauriculovertebral spectrum with the encephalocele expressed anteriorly.

Skeletal Alterations

Cervical vertebral fusions occur in 20 to 35 percent of cases, whereas platybasia and occipitalization of the atlas are found in about 30 percent. Complex vertebral anomalies below the level of the cervical spine are more common in patients with demonstrated cervical spine anomalies (Rollnick et al, 1987). Spina bifida; hemivertebrae; butterfly; fused or hypoplastic vertebrae; scoliosis; and anomalous ribs such as agenesis, duplication, fusion, or supernumerary ribs occur in at least 30 percent. Talipes equinovarus has been reported in about 20 percent. Radial limb anomalies have been noted in several cases. These may take the form of hypoplasia or aplasia of the radium and/or thumb (Gorlin et al, 1963; Bowen et al, 1971; Mandelcorn et al, 1971; Sugiura, 1971; Wilson, 1983; Figueroa and Friede, 1985; Mendelberg et al, 1985).

Cardiovascular Anomalies

Congenital heart defects are common and are reported to vary from 5 to 58 percent (Friedman and Saraclar, 1974; Greenwood et al, 1974; Gorlin et al, 1976; Shokeir, 1977; Pierpont et al, 1982; Tenconi and Hall, 1983; Wilson, 1983; Rollnick et al, 1987). Ventricular septal defect or tetralogy

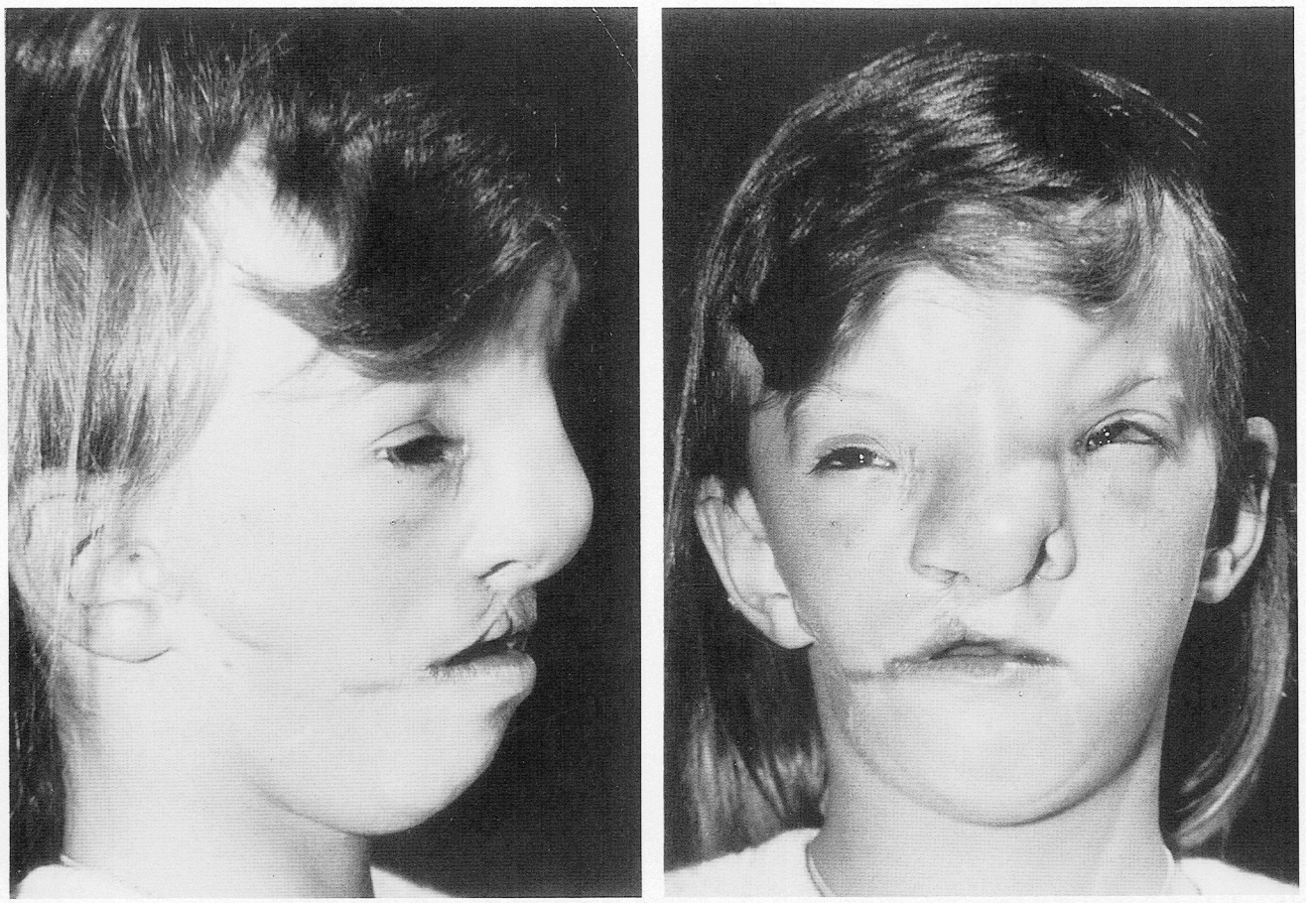

FIGURE 9 Combined features of Goldenhar complex and frontonasal dysplasia. Note ocular hypertelorism, colobomatous nostril, macrostomia, repaired cleft lip, facial asymmetry, epibulbar dermoid (left eye), and posteriorly angulated ear with surgically removed ear tags. From Fleischer-Peters A. (1969). Goldenhar syndrom und Kiefermissbildungen. Dtsch Zahnarztl Z 24:545–551.

of Fallot with or without a right aortic arch account for about 50 percent of the defects, although no single cardiac lesion is characteristic. Other anomalies may include transposition of the great vessels, tubular hypoplasia of the aortic arch associated with mild coarctation of the aorta, isolation of the left innominate artery with patent ductus arteriosus, pulmonic stenosis, and dextrocardia. A number of additional defects have been reported. Hypoplasia of the external carotid artery has also been noted.

Other Anomalies

Pulmonary anomalies range from incomplete lobulation, to hypoplastic lungs, to agenesis. Defects may be unilateral or bilateral. When unilateral, the defect is usually ipsilateral to the facial anomalies (Opitz and Faith, 1969; Gorlin et al, 1976; Bowen and Parry, 1980; Pierpont et al, 1982). Tracheoesophageal fistula has also been documented (Bowen and Parry, 1980). A variety of renal abnormalities have been reported, including absent kidney, double ureter, crossed renal ectopia, anomalous blood supply to the kidney, hydronephrosis, hydroureter, and other defects (Bowen et al, 1971; Shokeir, 1977; Rollnick et al, 1987). Imperforate anus with or without rectovaginal fistula has been described (Bowen et al, 1971).

OVERLAPPING CONDITIONS

A number of conditions commonly differentiated from oculoauriculovertebral spectrum have overlapping relationships in some instances. The combination of frontonasal dysplasia (Cohen et al, 1971) with epibulbar dermoids, ear tags, and ear anomalies (see Fig. 9) (Gupta et al, 1968; Fleischer-Peters, 1969; Tenconi and Hall, 1983; Musarella and Young, 1986) has already been discussed.

The branchio-oto-renal syndrome is associated with mixed hearing loss, preauricular pits, branchial fistulas, ear anomalies, malformations of the middle and inner ear, lacrimal duct stenosis, and renal dysplasia. Inheritance is autosomal dominant with high penetrance and variable expression (Fraser et al, 1978; Heimler and Lieber, 1986). Families have been described in which first degree relatives have varying features of hemifacial microsomia and/or BOR syndrome, thereby suggesting that, in some instances, hemifacial microsomia may constitute a component at the severe end of the BOR spectrum (Rollnick and Kaye, 1985).

Townes-Brocks syndrome consists of dysplastic ears, ear tags, and hearing loss in addition to thumb malformations, anal defects, and renal anomalies. Inheritance is autosomal dominant (Walpole and Hockey, 1982). Some cases bear resemblance to oculoauriculovertebral spectrum.

Wildervanck syndrome consists of fused cervical vertebrae, sensorineural hearing loss, and abducens paralysis with retracted globes (Duane syndrome). Some cases show overlap with oculoauriculovertebral spectrum (Franceschetti and Klein, 1954; Kirkham, 1969; Cross and Pfaffenbach, 1972).

DiGeorge sequence can be minimally expressed as the III-IV pharyngeal pouch complex in which there is absence or hypoplasia of the thymus, parathyroid glands, or both. It may be maximally expressed with cardiovascular anomalies, especially interrupted aortic arch and truncus arteriosus, and various craniofacial anomalies including micrognathia, ear anomalies, and cleft palate. The condition is known to be etiologically heterogeneous (Conley et al, 1979; Lammer and Opitz, 1986). Features of DiGeorge sequence may overlap with hemifacial microsomia.

Characteristics of the VATER association (*v*ertebral anomalies, ventricular septal defects, *a*nal atresia, *T-E* fistula with esophageal atresia, and *r*adial and renal dysplasia) (Quan and Smith, 1973), the CHARGE association (*c*oloboma, *h*eart disease, *a*tresia choanae, *r*etarded growth and development, *g*enital anomalies, and *e*ar anomalies and/or hearing loss) (Pagon et al, 1981; Siebert et al, 1985; Davenport et al, 1986), and the MURCS association (*Mü*llerian duct aplasia, *r*enal aplasia, and *c*ervicothoracic *s*omite dysplasia) (Duncan et al, 1979) sometimes overlap with oculoauriculovertebral spectrum.

References

Aleksic S, Budzilovich G, Chandra-Sekhar H, Reuben R, Boal D, McCarthy JM, Converse JM, Feigin I. (1976). Congenital facial neuropathy in oculoauriculovertebral dysplasia–hemifacial microsomia (Goldenhar-Gorlin syndrome). Bull Los Ang Neur Soc 41:68–77.

Aleksic S, Budzilovich G, Choy A, Reuben R, Randt C, Converse JM, McCarthy J, Feigin I. (1976). Congenital ophthalmoplegia in oculoauriculovertebral dysplasia–hemifacial microsomia (Goldenhar-Gorlin syndrome). Neurology NY 26:638–644.

Aleksic S, Budzilovich G, Greco MA, Epstein F, Feigin I, Pearson J. (1983). Encephalocele (cerebellocele) in the Goldenhar-Gorlin syndrome. Eur J Pediatr 140:137–138.

Aleksic S, Budzilovich G, Greco MA, Reuben J, Margolis S. (1984). Intracranial lipomas, hydrocephalus and other CNS anomalies in oculoauriculo-vertebral dysplasia (Goldenhar-Gorlin syndrome). Child's Brain 11:285–297.

Aleksic S, Budzilovich G, Reuben R, Lanuna J, McCarthy J, Converse JM, Feigin I. (1975). Unilateral arhinencephaly in Goldenhar-Gorlin syndrome. Dev Med Child Neurol 17:498–504.

Aouchiche M, Boyer Nouar A. (1972). Results of karyotype analysis in Goldenhar's syndrome. Bull Soc Ophthalmol Fr 85:57–69.

Baum JL, Feingold M. (1973). Ocular aspects of Goldenhar's syndrome. Am J Ophthalmol 75:250–257.

Bennun RD, Mulliken JB, Kaban LB, Murray JE. (1985). Microtia: a microform of hemifacial microsomia. Plast Reconstr Surg 76:859–865.

Berkman MD, Feingold M. (1968). Oculoauriculovertebral dysplasia (Goldenhar's syndrome). Oral Surg 25:408–417.

Bersu ET, Ramirez-Castro JL. (1977). Anatomical analysis of the developmental effects of anueploidy in man. The 18 trisomy syndrome: I. Anomalies of the head and neck. Am J Med Genet 1:173–193.

Berthelon S, Cremer N. (1969). Syndrome de Goldenhar avec malformations associets. Bull Soc Belg Ophthalmol 149:509–513.

Bock RH. (1961). Ein fall von epibulbärem dermolipome mit missbildungen einer gesichtshälfte. Diskordantes vorkommen bei einem eineiigen zwillingspaar. Ophthalmologica 155:86–90.

Boles DJ, Bodurtha J, Nance WE. (1987). Goldenhar complex in discordant monozygotic twins: a case report and review of the literature. Am J Med Genet 28:103–109.

Bowen AD, Parry WH. (1980). Bronchopulmonary foregut malformation in the Goldenhar anomalad. Am J Roentgenol 134:186–188.

Bowen DI, Collum LMT, Rees DO. (1971). Clinical aspects of oculoauriculo-vertebral dysplasia. Br J Ophthalmol 55:145–154.

Burck U. (1983). Genetic aspects of hemifacial microsomia. Hum Genet 64:291–296.

Caronni EP. (1967). La displasia auricolare branchiogena. Chir Ital 19:1231–1235.

Christiaens RF, Waldbaum R, Farriaux JP, La Fontaine JP. (1966). A propos de deux cas de dysplasie oculo-auriculovertebrale. Pediatrie 21:935–942.

Clarren SK, Salk DJ. (1983). Chromosome studies in hemifacial microsomia with radial ray defect. Am J Med Genet 15:169–170.

Cohen MM Jr. (1971). Variability versus "incidental findings" in the first and second branchial arch syndrome: unilateral variants with anophthalmia. Birth Defects Original Article Series 7(7):103–108.

Cohen MM Jr. (1982). The patient with multiple anomalies. New York: Raven Press.

Cohen MM Jr, Sedano HO, Gorlin RJ, Jirásek JE. (1971). Frontonasal dysplasia (median cleft face syndrome): comments on etiology and pathogenesis. Birth Defects Original Article Series 7(7):117–119.

Conley ME, Beckwith JB, Mancer JFK, Tenckhoff L. (1979). The spectrum of the DiGeorge syndrome. J Pediatr 94:883–890.

Connor JM, Fernandez C. (1984). Genetic aspects of hemifacial microsomia. Hum Genet 68:349.

Converse JM, Coccaro PJ, Becker M, Wood-Smith D. (1973). On hemifacial microsomia. The first and second branchial arch syndrome. Plast Reconstr Surg 51:268–279.

Cordier J, Stricker M, Reny A, Raspiller A. (1970). Syndrome de Franceschetti-Goldenhar discordant chez deux, jumelles monozygotes. Arch Ophthalmol (Paris) 30:321–328.

Cross HE, Pfaffenbach DD. (1972). Duane's retraction syndrome and associated congenital malformations. Am J Ophthalmol 73:442–449.

Curran JP, Al-Salihi FL, Allderdice PW. (1970). Partial deletion of the long arm of chromosome E-18. Pediatrics 46:721–729.

Davenport SLH, Hefner MA, Mitchell JA. (1986). The spectrum of clinical features in CHARGE syndrome. Clin Genet 29:298–310.

Duncan PA, Shapiro LR, Stangel JJ, Klein RM, Addonizio JC. (1979). The MURCS association: Müllerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia. J Pediatr 95:399–402.

Dyggve HV, Mikkelsen M. (1965). Partial deletion of the short arms of a chromosome of the 4-5 group (Denver). Arch Dis Child 40:82–85.

Ebbesen F, Petersen W. (1982). Goldenhar's syndrome: discordance in monozygotic twins and unusual anomalies. Acta Paediatr Scand 71:685–687.

Figueroa AA, Friede H. (1985). Craniovertebral malformations in hemifacial microsomia. J Craniofac Genet Dev Biol (suppl 1):167–178.

Figueroa AA, Pruzansky S. (1982). The external ear, mandible and other components of hemifacial microsomia. J Max Fac Surg 10:200–211.

Fleischer-Peters A. (1969). Goldenhar syndrom und kiefermissbildungen. Dtsch Zahnarztl Z 24:545–551.

Franceschetti A, Klein D. (1954). Dysmorphie cervico-oculo-faciale avec surdité familiale. (Klippet-Feil, retractio bulbi, asymetrie craniofaciale et autres anomalies congenitales). J Génét Hum 3:176–183.

François J, Haustrate L. (1954). Anomalies colobomateuses du globe oculaire et syndrome du premier arc. Ann Ocul 187:340–368.

Fraser FC, Ling D, Clogg D, Nogrady B. (1978). Genetic aspects of the BOR syndrome—branchial fistulas, ear pits, hearing loss, and renal anomalies. Am J Med Genet 2:241–252.

Friedman S, Saraclar M. (1974). The high frequency of congenital heart disease in oculo-auriculo-vertebral dysplasia (Goldenhar's syndrome). J Pediatr 85:873–874.

Goldenhar M. (1952). Associations malformatives de l'oeil et de l'oreille, in particular le syndrome dermoide epibulbaire-appendices auriculares-fistula auris congenita et ses relations avec la dysostose mandibulo-faciale. J Genet Hum 1:243–282.

Gómez-García A, Vargas-Torcal F, Paya-Abad EA. (1984). Sindrome de Goldenhar. Discordancia en gemelos monocigotos. An Esp Pediatr 20:400–402.

Gorlin RJ, Jue KL, Jacobson NP, Goldschimdt E. (1963). Oculoauriculovertebral dysplasia. J Pediatr 63:991–999.

Gorlin RJ, Pindborg J. (1964). Syndromes of the head and neck. 1st ed. New York: McGraw-Hill:261–265, 419–425.

Gorlin RJ, Pindborg J, Cohen MM Jr. (1976). Oculoauriculovertebral

dysplasia. In: Syndromes of the head and neck. 2nd ed. New York: McGraw-Hill:546–552.
GRABB WC. (1965). The first and second branchial arch syndrome. Plast Reconstr Surg 36:485–508.
GRAYSON BH, BORAL S, EISIG S, KOLBER A, MCCARTHY JG. (1983). Unilateral craniofacial microsomia. I. Mandibular analysis. Am J Orthodont 84:225–230.
GREENBERG F, HERMAN G, STAL S, GRUBER H, LEDBETTER DH. (1987). Chromosome abnormalities associated with facio-auriculo-vertebral dysplasia. Paper presented at the Clinical Genetics Conference, Minneapolis, MN, July 19–22.
GREENWOOD RD, ROSENTHAL A, SOMMER A, WOLFF G, CRAENEN J. (1974). Cardiovascular malformations in oculoauriculovertebral dysplasia. J Pediatr 85:816–818.
GRIX A JR. (1982). Malformations in infants of diabetic mothers. Am J Med Genet 13:131–137.
GUPTA JS, GUPTA SD, PRASHAR SK. (1968). Oculoauricular vertebral dysplasia. Br J Ophthalmol 52:346–347.
GUSTAVSON EE, CHEN H. (1985). Goldenhar syndrome, anterior encephalocele and aqueductal stenosis following fetal primidone exposure. Teratology 32:13–17.
HALL BD. (1979). Syndromes and situations simulated by amniotic bands. Paper presented at the Birth Defects Conference, Chicago, IL, June 24–27.
HEIMANN K VON. (1968). Beitrag zur klinik des Goldenhar syndroms. Klin Monatsbl Augenheilkd 152:686–692.
HEIMLER A, LIEBER E. (1986). Branchio-oto-renal syndrome: reduced penetrance and variable expressivity in four generations of a large kindred. Am J Med Genet 25:15–27.
HERMAN GE, GREENBERG F, LEDBETTER DH. (1988). Multiple congenital anomaly/mental retardation (MCA/MR) syndrome with Goldenhar complex due to a terminal del(22q). Am J Med Genet 29:909–915.
HERRMANN J, OPITZ JM. (1969). A dominantly inherited first arch syndrome. Birth Defects Original Article Series 5(2):110–112.
HODES ME, GLEISER S, DEROSA GP, YUNE HY, GIROD DA, WEAVER DD, PALMER CG. (1981). Trisomy 7 mosaicism and manifestations of Goldenhar syndrome with unilateral radial hypoplasia. J Craniofac Genet Dev Biol 1:49–55.
HOFFMAN-EGG L, VELISSAROPOULOS P. (1953). Malformation oculoauriculaire (lipodermoïde épibulbaire, appendices préauriculaires, colobome de la paupière supérieure) et leur relation avec de la dysostose mandibulofaciale. Ann Ocul 186:155–164.
HOLLWICH F, VERBECK B. (1969). Zur dysplasia oculoauricularis (Franceschetti-Goldenhar). Klin Monatsbl Augenheilkd 154:430–443.
HOO JJ, LORENZ R, FISCHER A, FUHRMANN W. (1982). Tiny interstitial duplication of proximal 7q in association with a maternal paracentric inversion. Hum Genet 62:113–116.
IDE CH, MILLER GW, WOHLSCHLAEGER P. (1970). Familial facial dysplasia. Arch Ophthalmol 84:427–432.
ISRAEL J, VASAN V, DOLEZAL E, RUBENSTEIN J, SZATKOWSKI M. (1987). Goldenhar complex (oculoauricular vertebral anomaly) in an infant of a diabetic: case report. Paper presented at the Clinical Genetics Conference, Minneapolis, MN, July 19–22.
JOHNSON JP, FINEMAN RM. (1982). Branchial arch malformations in infants of diabetic mothers: two case reports and a review. Am J Med Genet 13:125–130.
JONGBLOET PH. (1968). Considerations on the aetiology of Goldenhar's syndrome and related congenital dysplasias including chromosomal aberrations. Maandschr Kindergeneeskd 36:352–367.
JONGBLOET PH. (1987). Goldenhar syndrome and overlapping dysplasias, in vitro fertilization and ovopathy. J Med Genet 24:616–620.
KAYE CI, ROLLNICK BR. (1989). Personal observation.
KAYE CI, ROLLNICK BR, PRUZANSKY S. (1979). Malformations of the auricle: isolated and in syndromes' IV. Cumulative pedigree data. Birth Defects Original Article Series 15(5C):163–169.
KENNEDY LA, PERSAUD TVN. (1977). Pathogenesis of developmental defects induced in the rat by amniotic sac puncture. Acta Anat 97:23–24.
KIRKE DK. (1970). Goldenhar's syndrome: two cases of oculoauriculovertebral dysplasia occurring in full-blood Australian aboriginal sisters. Aust Pediatr J 6:213–214.
KIRKHAM TH. (1969). Cervico-oculo-acousticus syndrome with pseudopapilloedema. Arch Dis Child 44:504–508.
KUSHNICK T, COLONDRILLO M. (1975). 49,XXXXY patient with hemifacial microsomia. Clin Genet 7:442–448.
LADEKARL S. (1968). Combination of Goldenhar syndrome with the cridre-chat syndrome. Acta Ophthamol (KBH) 46:605–610.
LAMMER EJ, CHEN DT, HOAR RM, AGNISH ND, BENKE PJ, BRAUN JT, CURRY CJ, FERNHOFF PM, GRIX AW, LOTT IT, RICHARD JM. (1985). Retinoic acid embryopathy. N Engl J Med 313(14):837–841.
LAMMER EJ, OPITZ J. (1986). The DiGeorge anomaly as a developmental field defect. Am J Med Genet (suppl)2:113–127.
LIVINGSTON G. (1965). Congenital ear abnormalities due to thalidomide. Proc R Soc Med 58:493–497.
LOEVY HT, SHORE SW. (1985). Dental maturation in hemifacial microsomia. J Craniofac Genet Dev Biol (suppl 1):267–272.
LUCE EA, MCGIBBON B, HOOPER JE. (1977). Velopharyngeal insufficiency in hemifacial microsomia. Plast Reconstr Surg 60:602–606.
MANDELCORN MS, MERIN S, CALDARELLI J. (1971). Goldenhar syndrome with phocomelia. Am J Ophthalmol 72:618–621.
MANSOUR AM, WANG F, HENKIND P, GOLDBERG R, SHPRINTZEN R. (1985). Ocular findings in the facio-auriculovertebral sequence (Goldenhar-Gorlin syndrome). Am J Ophthalmol 100:555–559.
MARGOLIS S, ALEKSIC S, CHARLES N, GRECO MA, BUDZILOVICH G. (1984). Retinal and optic nerve findings in Goldenhar-Gorlin syndrome. Ophthalmology 91:1327–1333.
MCKENZIE J. (1958). The first arch syndrome. Arch Dis Child 33:477–486.
MELNICK M. (1980). The etiology of external ear malformations and its relation to abnormalities of the middle ear, inner ear and other organ systems. Birth Defects Original Article Series 16(4):303–331.
MELNICK M, MYRIANTHOPOULOS NC. (1979). External ear malformations: epidemiology, genetics and natural history. New York: Alan R. Liss:21.
MENDELBERG A, ARIEL I, MOGLE P, ARAD I. (1985). Tracheo-oesophageal anomalies in the Goldenhar anomalad. J Med Genet 22:149–150.
MICHAUD C, SHERIDAN S. (1974). Goldenhar's syndrome associated with cranial and neurological malformations. Can J Ophthalmol 9:347–350.
MIEHLKE A, PARTSCH CJ. (1963). Ohrmissbildung, facialis-und abducenslähmung als syndrom der thalidomidschadigung. Arch Ohrenheilkd 181:154–174.
MILLER MT. (1985). Association of Duane retraction syndrome with craniofacial malformations. J Craniofac Genet Dev Biol (suppl 1):273–282.
MOESCHLER J, CLARREN SK. (1982). Familial occurrence of hemifacial microsomia with radial limb defects. Am J Med Genet 12:371–375.
MOORE CA, WILROY RS, TONKIN I. (1987). Absence of the internal carotid in association with hemifacial defects and unilateral hydranencephaly. Paper presented at the Eighth Annual Workshop on Malformations and Morphogenesis, Greenville, SC, August 15–19.
MOUNOUD RL, KLEIN D, WEBER F. (1975). A propos d'un cas de syndrome de Goldenhar. J Génét Hum 23:135–154.
MURPHY MJ, RISK WS, VAN GILDER JC. (1980). Intracranial dermoid cyst in Goldenhar's syndrome. J Neurosurg 53:408–411.
MUSARELLA MA, YOUNG ID. (1986). A patient with median cleft face anomaly and bilateral Goldenhar anomaly. Am J Med Genet (suppl 2):135–141.
NEU KW, FRIEDMAN JM, HOWARD-PEEBLES PN. (1982). Hemifacial microsomia in cri du chat (5p-) syndrome. J Craniofac Genet Dev Biol 2:295–298.
OPITZ JM, FAITH GC. (1969). Visceral anomalies in an infant with the Goldenhar syndrome. Birth Defects Original Article Series 5(2):104–105.
PAGON RA, GRAHAM JM, ZONANA J, YONG S-L. (1981). Coloboma, congenital heart disease, and choanal artesia with multiple anomalies: CHARGE association. J Pediatr 99:223–227.
PAPP Z, GARDÓ S, WALAWSKA J. (1974). Probably monozygotic twins with discordance for Goldenhar syndrome. Clin Genet 5:86–90.
PASHAYAN H, PINSKY L, FRASER FC. (1970). Hemifacial microsomia–oculo-auriculo-vertebral dysplasia. A patient with overlapping features. J Med Genet 7:185–188.
PAULI R, JUNG JH, MCPHERSON EW. (1983). Goldenhar association and cranial defects. Am J Med Genet 15:177–179.
PEREZ ALVAREZ F, MARTINEZ SANTANA S, SIN OPI JM, HUERTA RODRIGUEZ J, LIERN CABALLERO M. (1984). Sindrome otocraneofacial asimetrico (microsomia hemifacial) in gemelos monocigoticos discordantes. Aspectos otologicos. An Esp Pediatr 21(8):769–773.
PIERPONT MEM, MOLLER JM, GORLIN RJ, EDWARD JE. (1982). Congenital cardiac, pulmonary and vascular malformations in oculoauriculovertebral dysplasia. Pediatr Cardiol 2:297–302.

POONAWALLA HH, KAYE CI, ROSENTHAL IM, PRUZANSKY S. (1980). Hemifacial microsomia in a patient with Klinefelter syndrome. Cleft Palate J 17:194–196.

POSWILLO D. (1973). The pathogenesis of the first and second branchial arch syndrome. Oral Surg 35:302–329.

POSWILLO D. (1974). Otomandibular deformity: pathogenesis as a guide to reconstruction. J Maxillofac Surg 2:64–72.

POSWILLO D. (1975). Hemorrhage in development of the face. Birth Defects Original Article Series 11(7):61–81.

QUAN L, SMITH DW. (1973). The VATER association. J Pediatr 82:104–106.

RAPIN I, RUBEN RJ. (1976). Patterns of anomalies in children with malformed ears. Laryngoscope 86:1469–1502.

REGENBOGEN L, GODEL V, GOYA V, GOODMAN RM. (1982). Further evidence for an autosomal dominant form of oculoauriculovertebral dysplasia. Clin Genet. 21:161–167.

ROBINSON LK, HOYME HE, EDWARDS DK, JONES KL. (1987). The vascular pathogenesis of unilateral craniofacial defects. J Pediatr 111:236–239.

ROLLNICK BR. (1988). Oculoauriculovertebral anomaly: variability and causal heterogeneity. Am J Med Genet (suppl 4):41–53.

ROLLNICK BR, KAYE CI. (1983). Hemifacial microsomia and variants: pedigree data. Am J Med Genet 15:233–253.

ROLLNICK BR, KAYE CI. (1985). Hemifacial microsomia and the branchio-oto-renal syndrome. J Craniofac Genet Dev Biol (suppl 1):287–295.

ROLLNICK BR, KAYE CI. (1987). Letter to the editor. Branchio-oto-renal syndrome: reduced penetrance and variable expressivity in four generations of a large kindred. Am J Med Genet 27:233.

ROLLNICK BR, KAYE CI, NAGATOSHI K, HAUCK W, MARTIN AO. (1987). Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. Am J Med Genet 26:361–375.

ROSENDAL TH. (1965). Aplasia-hypoplasia of the otic labyrinth after thalidomide. Acta Radiol 3:225–236.

ROSS RB. (1975). Lateral facial dysplasia (first and second branchial arch syndrome, hemifacial microsomia). Birth Defects Original Article Series 11(7):51–59.

RUNE B, SARNAS KV, SELVIK G, JACOBSSON S. (1981). Growth in hemifacial microsomia studied with the aid of roentgen stereophotogrammetry and metallic implants. Cleft Palate J 17:128–146.

RYAN CA, FINER NN, IVES E. (1988). Discordance of signs in monozygotic twins concordant for the Goldenhar anomaly. Am J Med Genet 29:755–761.

SALLER DN JR, MULLINS KEENE CL, RAFFEL LJ. KOSTRUBIAK IS, SUN CC. (1988). Prenatal diagnosis of severe hydrocephalus in a case of hemifacial microsomia. Am J Hum Genet (suppl 43):989.

SARAUX H, GRIGNON JL, DHERMY P. (1963). A propos d'une observation familiale de syndrome de Franceschetti-Goldenhar. Bull Soc Ophthalmol Fr 63:705–707.

SARAUX MH, BESNAINOU L. (1965). Les syndrome maxillooculaires. Ann Ocul 198:953–964.

SCHROETER C, JAHRIG K, WEINKE I. (1980). Ein neuer Fall von pentasomie X. Helv Paediatr Acta 35:233–241.

SETZER ES, RUIZ-CASTANEDA N, SEVERN C, RYDEN S, FRIAS JL. (1981). Etiologic heterogeneity in the oculoauriculovertebral syndrome. J Pediatr 98:88–90.

SHOKEIR MHK. (1977). The Goldenhar syndrome: a natural history. Birth Defects Original Article Series 13(3C):67–83.

SHPRINTZEN RJ. (1982). Palatal and pharyngeal anomalies in craniofacial syndromes. Birth Defects Original Article Series 18(1):53–78.

SHPRINTZEN RJ, CROFT CB, BERKMAN MD, RAKOFF SJ. (1980). Velopharyngeal insufficiency in the facio-auriculovertebral malformation complex. Cleft Palate J 17:132–137.

SIEBERT JR, GRAHAM JM, MACDONALD C. (1985). Pathological features of the CHARGE association: support for involvement of the neural crest. Teratology 31:331–336.

SMITH DW. (1982). Recognizable patterns of human malformation, 3rd ed. Philadelphia: WB Saunders, 497–500.

SOLTAN HC, HOLMES LB. (1986). Familial occurrence of malformations possibly attributable to vascular abnormalities. J Pediatr 109:112–114.

STARK RB, SAUNDERS DE. (1967). The first branchial syndrome: the oral-mandibular-auricular syndrome. Plast Reconstr Surg 29:229–239.

STOLL C, ROTH MP, DOTT B, BIGEL T. (1984). Discordance for skeletal and cardiac defect in monozygotic twins. Acta Genet Med Gemellol 33:501–504.

SUGAR HS. (1967). An unusual example of the oculoauriculovertebral dysplasia syndrome of Goldenhar. J Pediatr Ophthalmol 4:9–12.

SUGIURA Y. (1971). Congenital absence of the radius with hemifacial microsomia, VSD, and crossed renal ectopia. Birth Defects Original Article Series 7(7):109–115.

SUJANSKY E, SMITH ACM. (1981). Recombinant chromosome 18 in two male sibs with first and second branchial arch syndrome. Am Soc Hum Genet (abstracts) 92A.

SULIK KK, JOHNSTON MC, SMILEY SJ, SPEIGHT HS, JARVIS BE. (1987). Mandibulofacial dysostosis (Treacher Collins syndrome): a new proposal for its pathogenesis. Am J Med Genet 27:359–372.

SULIK KK, SMILEY SJ, TURVEY TA, SPEIGHT HS, JOHNSTON MC. (1989). Pathogenesis of cleft palate in Treacher Collins, Nager, and Miller syndromes. Cleft Palate J 26:209–215.

SUMMITT R. (1969). Familial Goldenhar syndrome. Birth Defects Original Article Series 5(2):106–109.

TAYSI K, MARSH JL, WISE DM. (1983). Familial hemifacial microsomia. Cleft Palate J 20:47–53.

TENCONI R, HALL BD. (1983). Hemifacial microsomia: phenotypic classification, clinical implications and genetic aspects. In: Harvold EP, ed. Treatment of hemifacial microsomia. New York: Alan R. Liss, 39–49.

TER HAAR B. (1972). Oculo-auriculo-vertebral dysplasia (Goldenhar's syndrome). Concordant in identical twins. Acta Med Genet (Roma) 21:116–124.

THOMAS P. (1980). Goldenhar syndrome and hemifacial microsomia: observations on three patients. Eur J Pediatr 133:287–292.

TIMM G. (1960). Zur morphologie des auges bei missbildungssyndromen. Klin Monatsbl Augenheilkd 137:557–571.

TOWNES PL, WHITE MR. (1978). Inherited partial trisomy 8q (22qter). Am J Dis Child 132:498–501.

VIRCHOW R. (1864). Über missbildungen am ohr und im bereich des ersten kiembogens. Virchows Arch Path Anat 30:221–234.

WALKER DG. (1961). Malformation of the face. Edinburgh: Livingstone.

WALPOLE IR, HOCKEY A. (1982). Syndrome of imperforate anus, abnormalities of hands and feet, satyr ears, and sensorineural deafness. J Pediatr 100:250–252.

WILSON GN. (1983). Cranial defects in Goldenhar's syndrome. Am J Med Genet 14:435–443.

WILSON GN, BARR M JR. (1983) Trisomy 9 mosaicism: another etiology for the manifestations of Goldenhar syndrome. J Craniofac Genet Dev Biol 3:313–316.

WILSON TG. (1958). A case of unilateral mandibulofacial dysostosis associated with agenesis of the homolateral lung. J Laryngol 72:238.

YOVICH JL, MULCAHY M, MATSON P. (1987). IVF and Goldenhar syndrome. J Med Genet 24:644.

YOVICH SL, STRANGER JD, GRAUAUG AA, LUNAY GG, DAWKINS RL, MULCAHY MT. (1985). Fetal abnormality (Goldenhar syndrome) occurring in one of triplet infants derived from in vitro fertilization with possible monozygotic twinning. In Vitro Fertil Embryo Transfer 2(1):27–32.