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RESEARCH ARTICLE

AN INSIGHT INTO - HEMIFACIAL MICROSOMIA

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Abstract

Hemifacial microsomia is a common birth defect involving first and second branchial arch derivatives. The phenotype is highly variable. In addition to craniofacial anomalies, there may be cardiac, vertebral, and central nervous system defects. Most cases are sporadic, but there are rare familial cases that exhibit autosomal dominant inheritance.

Introduction:-

The features of hemifacial microsomia include unilateral deformity of the external ear and small ipsilateral half of the face with epibulbar dermoid and vertebral anomalies. Coloboma of the upper eyelid is frequent. The ear deformities range from preauricular tags of cartilagenous masses, to atresia of the external auditory canal, anomalies in the size and shape of the external auricle, and even to anotia. Gorlin et al. (1963) suggested the designation oculoauriculovertebral dysplasia for this disorder.

Saraux et al. (1963) described 2 sisters with Goldenhar syndrome, born of healthy, unrelated parents. The karyotype was normal. Proto and Scullica (1966) described the condition in a father and his son and daughter. The mother was a first cousin of the father. A patient who possibly had the same condition was observed by Fraser (1967) to have acroosteolysis of the terminal phalanges. Krause (1970) described affected brother and sister. The proband had a hemangioma of the scalp. Rollnick and Kaye (1983) studied the families of 97 probands. Of 433 first-degree relatives, 35 (8%) had the same or a similar anomaly. Of 176 sibs, 11 (6%) were 'affected.' The most frequent anomaly was a mild ear malformation such as preauricular nodule or tag. Multifactorial determination was proposed. Rollnick et al. (1987) reviewed phenotypic characteristics of 294 patients.

Morrison et al. (1992) reviewed the cardiovascular anomalies associated with OAV dysplasia.

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Sutphen et al. (1995) found that 3 of 60 patients with the oculoauriculovertebral spectrum (OAVS) had tracheoesophageal fistula, with or without esophageal atresia.

Stoll et al. (1998) described a mother and 2 of her children who had the oculoauriculovertebral spectrum. The mother had only auricular anomalies for which she had had plastic and reconstructive surgery. Her first child, a girl, had a bilateral cleft lip and palate, a coloboma of the upper eyelid, facial asymmetry, and posteriorly angulated ears. This child also had bilateral vesicoureteral reflux. During the second pregnancy, her fetal ultrasonographic examination performed at the 18th week of gestation showed a cleft lip and palate. At the 31st week of gestation, clubfeet, hypoplasia of the left ear, hypoplasia of the left maxillary and mandibular arches, and left microphthalmia were evident. Examination of the male fetus after termination of the pregnancy confirmed the findings of ultrasonography and demonstrated vertebral anomalies.

Van Meter and Weaver (1996) reported 2 infants (a male and a female) with significant overlap of symptoms of oculoauriculovertebral spectrum and CHARGE association (214800). In addition, both infants had plagiocephaly and torticollis, and the boy had cleft lip, heminostril, and tracheoesophageal fistula. The authors suggested that deficiency in migration of neural crest cells, deficiency of mesodermal formation, or defective interaction between neural crest cells and mesoderm may explain the pathogenesis of these defects of blastogenesis.

Nijhawan et al. (2002) reported 7 children with Goldenhar syndrome who were found to have dysplastic, ectopic, or bilobed caruncles, a small body at the medial angle of the eye that contains modified sebaceous and sweat glands. Four of the children had a nasal sinus or tag and 1 had a nasal-ocular cleft, suggesting an abnormality in the developmental process that is common to the nose and caruncle.

By study of a series of 30 cases (26 previously reported) and by analysis of a congenital birth defects registry in Spain, Wang et al. (2002) found that infants of diabetic mothers were at increased risk for a diagnosis of OAVS. Analysis of the registry data gave an odds ratio of OAVS of 2.28 (95% CI, 1.03-4.82; P = 0.03) and 1.50 (95% CI, 0.08-9.99; P = 0.49) in maternal gestational diabetes and preconceptually diagnosed type I or II maternal diabetes, respectively. Wang et al. (2002) hypothesized that poorly controlled maternal diabetes interferes with neural crest cell migration.

Keegan et al. (2001) performed a retrospective analysis of 8 patients with HFM-expanded spectrum and anal anomalies to determine whether this subset had Townes-Brocks syndrome (TBS; 107480). Two patients had major phenotypic findings of TBS. Sequencing of the SALL1 gene (602218) in 4 of the 8 patients revealed 1 with a C-to-T transition resulting in the nonsense mutation arg276 to ter (602218.0003) at a mutation hotspot. Keegan et al. (2001) suggested that patients with overlapping features of both Townes-Brock syndrome and hemifacial microsomia-expanded spectrum should be screened for SALL1 mutations.

Derbent et al. (2003) described a child with del22q11 who had a phenotypic appearance similar to that seen in OAVS. He had left microtia with atresia of the external meatus, left mandibular hypoplasia, and peripheral facial nerve paralysis. Growth parameters were below the 5th percentile, but intelligence and ophthalmologic examination were normal. Cardiac findings included situs inversus dextrocardia, double outlet right ventricle, pulmonic stenosis, and ventricular septal defect. Radiographs showed platybasia, complete fusion of the C2-C3, and posterior fusion of the T1-T2 vertebrae.

Beck et al. (2005) described 2 unrelated girls with OAVS and ocular colobomas. One girl had bilateral iris colobomas extending into the retina and a small left optic nerve coloboma; her mother had features consistent with OAVS and a segmental area of heterochromia of her right iris. The second girl had a large left inferior chorioretinal coloboma involving her optic nerve and macula as well as a left colobomatous cyst; her sister and father had features consistent with OAVS, although neither had ocular colobomas.

Touliatou et al. (2006) reported detailed clinical features of 17 Greek patients with Goldenhar syndrome, including a pair of affected monozygotic twins. The most consistent findings were auricular defects (94%), followed by facial anomalies (76%), ocular anomalies (65%), and conductive hearing loss (76%). Most features were unilateral (70%); mandibular hypoplasia was ipsilateral to the dysplastic ear in 9 of 10 patients. Facial nerve paralysis and mental retardation were also observed.

Diagnosis

Prenatal Diagnosis

Castori et al. (2006) presented a case of OAVS diagnosed prenatally with multiple congenital anomalies and reviewed the prenatal ultrasound findings of 20 previously reported cases. Gestational age at diagnosis ranged from 14 to 35 weeks, and almost half of the cases were associated with either poly- or oligohydramnios. Facial structures were involved in 52% and included microphthalmia, ear anomalies, facial asymmetry, and facial cleft. Central nervous system defects occurred in 47% and included hydrocephalus, occipital encephalocele, and cerebellar hypoplasia. Congenital heart defects, primarily atrioventricular septal defects, occurred in 19%. Additional findings included hydroureteronephrosis, radial aplasia, and lung and kidney agenesis.

Pathogenesis

Using a statistical methodology, Kallen et al. (2004) attempted to identify a group of probable cases of OAV dysplasia and to investigate the possible relationships between different patterns of congenital malformations. Among 5,260 infants with multiple malformations collected from 4 large registers of congenital malformations, they identified 312 probable OAV cases. With the same technique, they had previously defined epidemiologic delineations of 3 other well-known nonrandom associations of congenital malformations: CHARGE, VATER (192350), and OEIS (258040). They found convincing relationships between OAV and VATER or CHARGE, but none between OAV and OEIS or between the 3 malformation complexes CHARGE, VATER, and OEIS. Kallen et al. (2004) suggested that the connection between OAV and CHARGE could be related to a common pathogenetic mechanism, namely, disturbed neural crest development.

Inheritance

Although most cases are sporadic and a few families consistent with autosomal recessive inheritance have been reported, other families clearly support autosomal dominant inheritance. For example, Regenbogen et al. (1982) described a kindred with 9 affected persons in 3 generations and 3 instances of male-to-male transmission. The authors found at least 4 other reported instances of presumed autosomal dominant inheritance. Summitt (1969) described a kindred with many affected persons in an autosomal dominant pattern including male-to-male transmission. Notable variability in the clinical picture was described. Regenbogen et al. (1982) suggested that eye involvement may be less marked in the dominant form. Godel et al. (1982) described an Oriental Jewish family with 9 affected persons in 3 generations, including 3 instances of male-to-male transmission. Ryan et al. (1988) observed the Goldenhar anomaly in both of presumably monozygotic twins, but severity was strikingly different. They referred to work suggesting that in some cases the Goldenhar anomaly results from fetal hemorrhage in the region of the first and second branchial arches at the time when the blood supply of these arches switches from the stapedial artery to the external carotid artery. Soltan and Holmes (1986) suggested a link between genetic causes and vascular disruption. They described 5 close relatives with different malformations usually attributed to vascular accidents, including 1 with congenital microtia with preauricular appendages, a possible variant of the Goldenhar anomaly.

Setzer et al. (1981) reported 2 pairs of discordant monozygotic twins and an instance of affected mother and son and mother's sister. They suggested genetic heterogeneity. Discordant monozygotic twins were reported by Burck (1983), who gave an extensive review of the literature. Connor and Fernandez (1984), who considered hemifacial microsomia to be identical with Goldenhar syndrome, reported discordant monozygotic twins. They assembled from the literature 14 monozygotic twin pairs of whom only 2 were concordant. Such would be consistent with a somatic mutation as the origin. Boles et al. (1987) observed a male twin pair discordant for epibulbar dermoids, auricular appendages, malformed auricles, and hemifacial microsomia. The twins were dichorionic but apparently monozygotic by blood grouping, cytogenetic, and dermatoglyphic criteria. Some 20 twin pairs in all have been reported in which at least 1 member exhibited the features of Goldenhar syndrome. All of the 5 monozygotic twin pairs for which placental information was available have been discordant and 2 of these had dichorionic membranes. The failure of discordant monozygotic twins to be limited to monochorionic pairs argues against the idea that developmental abnormalities arising from placental vascular anastomoses explain the discordant expression. Jongbloet (1987) suggested that sporadically occurring Goldenhar syndrome is the result of 'overripeness ovopathy' and that this and overlapping anomalies 'should be considered to be just casualties in the broad continuum of reproductive wastage seen in high risk conceptions.' He cited an example of Goldenhar syndrome in one of triplets derived from in vitro fertilization.

Kaye et al. (1992) analyzed the families of 74 probands. As the basis for segregation analysis, criteria used in evaluating relatives as affected were outlined. Relatives were examined to identify ear malformations, mandibular

anomalies, and other craniofacial abnormalities. They concluded that the hypothesis of no genetic transmission could be rejected; the evidence favored autosomal dominant inheritance, whereas recessive and polygenic models were not distinguishable.

Kobrynski et al. (1993) reviewed 13 chromosomal aberrations that had been described in association with the FAV sequence and added the case of an infant girl born with complete trisomy 22 and features of this disorder: left hemifacial microsomia, ear anomaly, and limbal and epibulbar complex choristoma.

Population Genetics
Gorlin (1990) estimated the incidence of HFM to be 1 in 5,6000.

Morrison et al. (1992) estimated a minimum prevalence rate of OAV dysplasia of 1 in 45,000 in Northern Ireland.

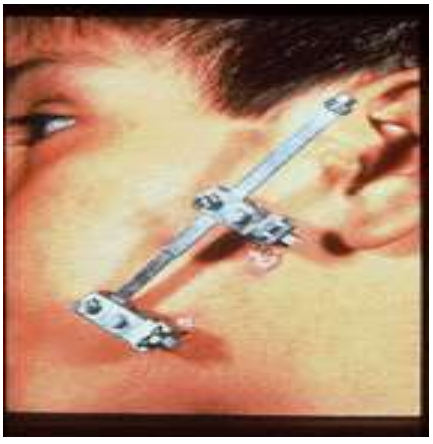
Mapping
Kelberman et al. (2001) performed a genomewide search for linkage in 2 families with features of HFM. In 1 family, the data were highly suggestive of linkage to a region of approximately 10.7 cM on chromosome 14q32, with a maximum multipoint lod score of 3.00 between microsatellite markers D14S987 and D14S65. Linkage to this region was excluded in the second family, suggesting genetic heterogeneity.

Molecular Genetics
Based on mapping, mouse expression, and phenotype data, Kelberman et al. (2001) considered the goosecoid gene (GSC; 138890) to be an excellent candidate gene for HFM. They searched the GSC coding region for mutations in 2 families segregating HFM and in 120 sporadic cases; none was found. They excluded gross rearrangements of the gene by Southern blot analysis.

In 4 patients with Goldenhar syndrome, Splendore et al. (2002) found no mutation in the TCOF1 gene (606847), which is mutant in Treacher Collins syndrome (154500).

Animal Model
Naora et al. (1994) described a transgenic mouse line that carries an autosomal dominant insertion mutation that results in hemifacial microsomia, including microtia and/or abnormal bite. The locus, designated Hfm for hemifacial microsomia-associated locus, was mapped to mouse chromosome 10 by in situ hybridization. By using sequences flanking the insert, the preintegration region was isolated. Analysis demonstrated that a deletion of at least 23 kb had occurred in association with the transgene integration. Homozygosity may result in prenatal lethality. They interpreted the results as suggesting that the Hfm gene is necessary for prenatal development.

Treatment
For these patients, treatment generally requires the expertise of both a craniofacial surgeon and an orthodontist with experience with these problems. The jaw deformity is addressed as early as 3 years of age if the mandibular retrusion is severe enough to cause airway difficulty. This jaw reconstruction can be achieved by extending the mandible with a rib graft or with the utilization of a distraction device.



The distraction of the mandible involves cutting the bones of the jaw (a corticotomy) and placing two pins on either side of the corticotomy. Each day, the pins are manually pushed apart and new bone is generated in the area of the corticotomy. The best approach to reconstructing the jaw is determined by the surgeon and is specific for each patient. If it is needed, ear reconstruction is performed in four stages and usually begin at the age of six years. Throughout life, these patients must maintain adequate dental occlusion through ongoing orthodontic treatment.

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