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Review of the etiologic heterogeneity of the oculo-auriculo-vertebral spectrum (Hemifacial Microsomia)*

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*This paper is dedicated to the memory of Dr Robert J. Gorlin and Dr David Bixler.

Structured Abstract

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Hemifacial microsomia is a congenital asymmetry of the lower face that may be associated with other cranial and extracranial anomalies. The variability of its severity, and wide range of anomalies that have been reported with it in some cases has resulted in these composite manifestations being given a number of names, including oculo-auriculo-vertebral spectrum (OAVS). Etiology is often stated to be a perturbation of embryonic blood flow in the developing region, although other factors may also play a role in some cases. Depending on what is considered to be minimum criteria for affected classification, what is often to be presumed to be a sporadic event in a family may be the more severe manifestation of a familial condition. Etiological factors are clearly heterogeneous, the investigation of which is confounded by not only the lack of a refined affected phenotype, but also the apparent influence of genetic factors in some instances that directly influence phenotype perhaps through alteration of mesodermal development, or indirectly through increased susceptibility to vascular disruption. Future studies likely to advance knowledge in this area will need to incorporate an analysis of who may be minimally affected in families, so that advances in genotyping will have greater power to distinguish genetic factors that may influence OVAS through interaction with environmental factors in particular families. The same genetic-environmental factors and or etiological mechanisms may then be investigated in apparently sporadic cases.

Key words: craniofacial genetics; Goldenhar syndrome; hemifacial microsomia; oculoauriculovertebral dysplasia; oculoauriculovertebral spectrum; orthodontics

Introduction

Nomenclature

In 1952, Goldenhar described three patients with epibulbar dermoids, pre-auricular skin tags mandibular asymmetry, and cervical vertebrae abnormalities. This combination of anomalies was subsequently called Goldenhar syndrome (1). In the 1960s Drs Gorlin and Pindborg defined hemifacial microsomia as a condition affecting aural, oral, and mandibular

development. They noted that the disorder varied from mild to severe, and that facial involvement was limited to one side in many, but not all cases. They considered Goldenhar syndrome to be a variant of this complex. In 1963, Gorlin *et al.* suggested the use of the term oculo-auriculo-vertebral dysplasia to describe the syndrome characterized by epibulbar dermoids and/or lipodermoids, auricular appendages, blind-ended auricular fistulas, and vertebral anomalies (2).

In 1976, Gorlin *et al.* concluded that there was so much overlap among the clinical manifestations of hemifacial microsomia, Goldenhar syndrome, and oculo-auriculo-vertebral dysplasia that no valid distinction among them could be made (3). Clinical cases with all or some of the features attributed to hemifacial microsomia and Goldenhar syndrome suggested a continuous spectrum instead of discrete diagnostic entities. Etiologic heterogeneity and complexity was suggested by the great variability observed in sporadic cases, and the occurrence of familial instances that occur with apparent Mendelian modes of inheritance. Thirty years later, there has really not been much to change in their assessment.

Subsequently, Gorlin *et al.* have used the term oculo-auriculo-vertebral spectrum (OAVS) to describe this 'complex' (4). The term OAVS was a significant step in the realization that cardiac, renal, skeletal, and other anomalies may occur in addition to those of facial structures; and there are patients with variable manifestations which represent a spectrum of developmental anomalies.

Emblematic of the variation in clinical manifestation, the theory or uncertainty of etiology, and the potential for confusion if reading the literature about congenital asymmetric abnormalities of the face that involve the mandible and ear are the additional names for this condition that include: first arch syndrome, first and second branchial arch syndrome, Goldenhar–Gorlin syndrome, lateral facial dysplasia, unilateral craniofacial microsomia, otomandibular dysostosis, unilateral intrauterine facial necrosis, auriculo-branchiogenic dysplasia, facio-auriculo-vertebral dysplasia, and facio-auriculo-vertebral malformation complex (4), and craniofacial microsomia (sometimes used to describe individuals who also have involvement of the upper face and forehead) (5). The term OAVS will be used in the rest of this paper unless there is reason to refer to another clinical name.

Epidemiology

The incidence has been estimated or reported to be 1/3500 (6), 1/5600 (7), and 1/26 550. The later is from a prospective newborn study by Melnick (8). Given the marked clinical expression of OAVS, cases with a minor effect may go undetected, and cases with additional cranial and especially extracranial anomalies may be given another diagnosis (9). An incidence of 1/5600 was thought by Gorlin *et al.* to be the best estimation (4).

Taking that value, the incidence of OAVS would be approximately half as common as cleft palate without cleft lip (based upon an incidence of 1/2500), and would be only one-fifth to one-sixth as common as cleft lip with or without cleft palate (based upon an incidence of 1/1000 in whites) (4). The incidence of craniosynostosis has been estimated to be 0.4/1000 (1/2500) (10), making OAVS the fourth most common human craniofacial anomaly after cleft lip with or without cleft palate, cleft palate, and craniosynostosis. Unlike cleft lip with or without cleft palate, the incidence of which can vary among ethnic groups, OAVS is more like cleft palate without cleft lip with a relatively consistent incidence among ethnic groups. The male:female ratio, and the ratio of right vs. left side involvement, is at least 3:2 for the former, and 3:2 for the later (4).

Etiology

The etiology of OAVS is heterogeneous. It remains to be determined if all or most of the etiologic factors converge on only one or a few mechanisms for the development of OAVS. One thing that should be consistent is that there is some effect on development in the region of the embryo that will give rise to the involved structures during a critical time of embryogenesis. The effect has most often been associated with some type of vascular perturbation and or neural crestopathy (11).

These etiologic factors include maternal vasoactive medication use (especially in conjunction with smoking) in the first 10 weeks of gestation, multiple gestations, e.g. twining (12), primidone embryopathy (13), retinoic acid embryopathy (14), thalidomide embryopathy (15), and maternal (pre-existing or gestational) diabetic embryopathy (12,16). Mothers of infants with OAVS (as well as other anomalies of unknown etiology) should be evaluated for diabetes to aid in counseling concerning cause and recurrence risks (12). Hemifacial

microsomia has also been reported in a number of other conditions, Mendelian syndromes, and different chromosome aberrations, some of which were mosaic (17).

Werler *et al*. addressed the concern that more infants with hemifacial microsomia were born to United States Gulf War veterans than expected (18). Odds ratios adjusted for family income, race, and body mass index in early pregnancy were determined using data collected from a case–control study of hemifacial microsomia to estimate risk in relation to parental military service and, in particular, Gulf War service. They identified affected cases who were 3 years old or younger at craniofacial clinics in 24 US cities and matched them to controls by age and pediatrician. The mothers of 232 cases and 832 controls were interviewed between April 1996 and November 2002 about pregnancy events and exposures, including military service before the child was born and Gulf War deployment 5–11 years before the child was born.

The parents of four (1.7%) cases and 23 (2.8%) controls served in the Gulf War [multivariate adjusted odds ratio (MVOR), 0.8; 95% confidence interval (CI), 0.3–2.3]. The MVOR for parental Gulf War service in the Army was 2.8 (95% CI, 0.8–9.6). The corresponding MVOR for any parental service in the Army was 2.4 (95% CI, 1.4–4.2), based on 22 cases and 45 controls. Although the odds ratio for service in the Army was independent of Gulf War service and was associated with a modest increase in risk of hemifacial microsomia, the risk in offspring was not associated with parental service in the Gulf War 5–11 years before birth. The authors noted that their findings of an increased risk for hemifacial microsomia for service in the Army in general may be confounded by unmeasured lifestyle factors.

In addition to the recognition that extracranial developmental anomalies could be associated with hemifacial microsomia in the OAVS, there is overlap of the clinical features in some patients with occurrences of developmental anomalies that are referred to as associations. In this use, an association is a number of developmental anomalies that occur together in a group of patients more often than would be expected by chance, i.e. the grouping or association of these developmental anomalies appear to be non-random. The distinction between an association and a syndrome is sometimes the subject of discussion, and often depends on the consistency of common occurrence, or knowing the etiology, of the anomalies. Separate anomaly components of developmental abnormality associations are often isolated occurrences, i.e. they occur in a patient without any associated major developmental anomaly and thus in that patient do not represent an association. However, when they do occur with at least some of the components of a pattern of other developmental anomalies more often than would be expected by chance, they can be considered as a part of the association (19).

Most developmental abnormality associations are known by acronyms that utilize part of the names of some of the associated developmental abnormalities, similar to OAVS. For example, the developmental anomalies often found in VATER association include Vertebral anomalies, Anal atresia, Tracheoesophageal atresia, and Radial anomalies. Later consideration of other developmental anomalies that occur often enough with the associated anomalies lead to the 'expansion' of VATER to VACTERL, standing for Vertebral anomalies, Anal atresia, Cardiac anomalies, Tracheoesophageal atresia, Renal anomalies, and Limb anomalies. The CHARGE association (now sometimes referred to as a syndrome) consists of coloboma, heart, atresia choanae, retardation of growth and development, genitourinary, and ear anomalies. The MURCS association involves variable developmental anomalies of the mullerian, unilateral renal, cervicothoracic, and somite structures or their derivatives. The OEIS association is defined by omphalocele, exstrophy of the cloaca, imperforate anus, and spinal anomalies (20).

Like developmental anomaly associations, developmental anomaly sequences can have a non-random pattern of associated anomalies that are connected embryologically with an initial anomaly that results in one or more subsequent anomalies. Klippel–Feil sequence (sometimes called Klippel–Feil syndrome) is a heterogeneous condition characterized by a defect in the formation or segmentation of the cervical vertebrae that can have associated anomalies. Caudal dysplasia sequence (also called caudal regression or caudal deficiency) is a another spectrum of anomalies involving the development of caudal structures that varies from incomplete development of the sacrum and to a lesser extent the lumbar vertebrae, to agenesis of these

structures along with severe deformities of the lower limbs along with soft tissue (popliteal) webbing from lack of movement secondary to neurological deficit at the cord level. Occasional anomalies seen with caudal dysplasia include renal agenesis, imperforate anus, cleft lip, cleft palate, microcephaly and meningomyelocele (20).

The point of briefly mentioning the preceding wide range of anomaly patterns is that there are individuals who are classified with one condition based upon features common to that condition, who also have some additional feature or features that overlap with other conditions. This overlap has been reported in individuals with OAVS and all of the developmental anomaly associations and sequences (VATER, etc.) previously mentioned (21–23). Stepping back and taking a broader look has resulted in the proposal that at a basic level these conditions may represent an abnormality in development that may result in anomalies that may be a part of a broad spectrum, such as the axial mesodermal dysplasia spectrum (22,24). Ultimately, this observation reinforces the heterogeneity of OAVS as well as other spectrums, associations and sequences of developmental anomalies, the oversimplification of placing a diagnosis with presumed etiology on a patient based upon observation of an anomaly, and the necessity for examining the patient with one anomaly for others that may be present, although not necessarily in the immediate proximity of the anomaly initially noted.

Familial occurrence, variable expressivity and genetic influences on susceptibility

Most cases of OAVS are said to be sporadic (i.e. only one person is affected in the family, often taken as being at least within three generations). However, Rollnick and Kaye showed that taking a careful history and clinical examination for dysmorphology in the relatives of the obviously affected individual who brought the family to attention (called the proband) revealed 45% of the 'non-affected' relatives to have some manifestation (an external ear anomaly or preauricular tissue tag being the most common) (25). Although their definition of what is an ear anomaly is open to discussion, this suggested that the OAVS is more often familial than generally appreciated; and that since most affected relatives had a mild expression or manifestation, the phenotypic spectrum is broad and variable with the likelihood that the most severe expressions of the disorder are rarer.

Rollnick *et al.* studied 294 individuals with oculoauriculovertebral dysplasia and 'variants' (26). The sample was divided into five subgroups based upon the presence of combinations of minimal diagnostic criteria, i.e. microtia, mandibular hypoplasia, anomalies of the cervical spine and/or epibulbar or lipodermoids. Microtia (small and/or malformed external ear) was the common minimal diagnostic criterion for inclusion. Individuals with recognized Mendelian disorders and chromosomal abnormalities were excluded, as were individuals with microtia and other craniofacial anomalies not observed in OAVS. The following data were recorded: 1) gender (M:F 191:103); 2) race (78% Caucasian); 3) the presence of unilateral or bilateral microtia (193 unilateral, 98 bilateral); 4) the presence of symmetric microtia in bilateral cases (34/98); 5) the presence of mandibular hypoplasia ipsilateral or contralateral to the microtic ear or most severely microtic ear in bilateral cases (135/137 were ipsilateral in unilateral cases, 55 of 62 were ipsilateral in bilateral cases); 6) the number of individuals with no other congenital anomaly in addition to the minimal diagnostic criteria (154/294), with only one other congenital anomaly (51/294), and with two or more other congenital anomalies (89/294); and 7) the type of other congenital anomalies.

The findings from this study included 1) mandibular asymmetry should be expected in patients with unilateral or bilateral microtia, grounds for the orthodontist to look for mandibular asymmetry in even relatively mild cases of microtia; 2) bilateral involvement is frequent in patients with microtia; 3) other malformations are seen frequently in all subgroups; 4) anomalies of the cervical spine are more likely to be associated with other anomalies; and 5) other malformations are seen in all systems and should be searched for to provide optimal management. It was also suggested that they should be searched for to maximally ascertain familial involvement and estimate the impact of inheritance on their occurrence.

Heterogeneity and a trend for genetic factors when present to influence susceptibility is suggested by the observation that most monozygotic (identical) twins are discordant for OAVS, and that when concordant may have varying manifestations (27). Additional families with OAVS involving more than one generation

have been identified, supporting the questioning of OAVS being without familial influence (28–31). The familial occurrence beyond monozygotic twins implies that there may be inherited genetic factors in some that increase susceptibility to OAVS anomalies resulting directly or indirectly in an abnormality of cell migration or tissue development.

The question of genetic influence was further investigated by Kaye *et al.* who performed a segregation analysis on 74 families of probands with OAVS anomalies, including 116 parents and 195 offspring (32). They rejected ($p < 10^{-8}$) the hypothesis of no genetic influence. Their data favored autosomal dominant inheritance; while recessive and polygenic models were not distinguishable from each other. Cousley and Wilson applied the stochastic single-gene model to hemifacial microsomia and suggested that a single gene mutation could be responsible (33).

Kelberman *et al.* applied a genome wide search for linkage in two families with features of hemifacial microsomia was performed to identify the disease loci (34). The heterogeneity of this condition, even when familial, was again underscored when data from one family 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; while linkage was excluded from this region in the second family. The important developmental gene Goosecoid is in region with linkage in the one family, and was thought to be an excellent candidate gene for hemifacial microsomia based on mouse expression and phenotype data. However, while not excluding all possible explanations for Goosecoid to influence hemifacial microsomia, there were no coding region mutations in the familial cases or in 120 sporadic cases.

These types of clinical studies turn on the definition of affected and unaffected individuals, indicating the need for more objective classification of proband relatives. Anthropometric morphometric analysis is needed to further refine the phenotypic spectrum in families (35), although the gene or genes involved in each family may be different.

Animal teratogen models

In a review by Everett and Hartsfield on mouse models for craniofacial anomalies including teratogenic models demonstrating an affect on a developmental field at a critical time of development it was noted that Poswillo used a mouse model in which triazene (the antifolate drug 3,3 dimethyl-1-triazene) was administered by intraperitoneal injection to pregnant CS1 mice (36,37). This resulted in a time of administration during development dependent hemorrhage of the stapedial artery, which is transiently present in fetal development, connecting the branches of the future external carotid artery to the internal carotid artery (38), resulting in underdevelopment of one or both sides of the craniofacies. This was referred to by Poswillo as first and second branchial arch syndrome.

Another indicator of the importance of the stage of development were otomandibular anomalies that occurred in macaque and marmoset monkeys following maternal intake of 10 mg/kg of thalidomide on days 20–25 of embryogenesis (39). Control and exposed specimens were obtained by hysterotomy from day 30 to 85 of development. There was no observable difference in the exposed specimens until day 32, at which time a dark stain appeared over the junction of the first and second branchial arch derivatives centered on the otic pit. This stain increased in intensity between days 33 and 35 before starting to resolve. Obvious differences in the development of the external ear cartilages could be observed in the affected specimens by day 45 when compared with the control specimens (40).

Padmanabhan and Singh found that a single dose of cyclophosphamide administered on day 12 of gestation to CF rats resulted in microtia in 97.5% of fetuses at term (41). Extensive hemorrhages were present in and around the region of the ears, which were low set and dorsally placed. Additional histological findings in affected embryos included persistence of the meatal plug, branching of the primordium of the external acoustic meatus, periotic hemorrhages, narrowing of the tympanic cavity, presence of only one or two primordia of the middle ear ossicles, and hypoplasia of the stapedial artery.

These models support the theory that one mechanism for development of branchial arch anomalies is when there is a disruption of the orderly development of the facial circulatory system. This disruption may be in an area dependent on the blood flow, or affected by the resolution of a hemorrhage, variably affecting a regional developmental field involving multiple tissues. The usual constellation of anomalies suggests the

origin of their development at approximately 30–45 days of human gestation, a critical period of embryogenesis (4). Further delineation of a disruption of embryonic blood supply as a sequential mechanism for producing developmental anomalies has been proposed with the subclavian artery supply disruption sequence as a possible etiology for the Poland, Klippel-Feil and Möbius anomalies (42,43).

An interference in chondrogenesis, regardless of the mechanism, has been postulated to be primarily responsible for the hemifacial microsomia phenotype. In support of this, it has been shown through surgical interference of mandibular development in the chick embryo asymmetrical perturbation of Meckel's cartilage has been shown to result in asymmetry of the mandible. It was proposed that, irrespective of cause, the skeletal pathogenesis of hemifacial microsomia primarily involves the auriculofacial cartilage model (33).

Animal genetic models

Investigation of the transgene insertion mutation *Hfm* (hemifacial microsomia-associated locus) mouse supports the hypothesis that at least a proportion of microtia and hemifacial microsomia occurrences have a genetic influence mediated via mesenchymal disruptions and possibly embryonic hemorrhages (33). This transgene insertion results in hemifacial microsomia, including microtia and/or abnormal occlusion, transmitted as an autosomal dominant trait (44). Offspring that carry the transgene insertion develop varying degrees of craniofacial malformation with about 25% individuals exhibiting hemifacial microsomia. It is particularly interesting that hemorrhage of the dorsal vasculature of the second branchial arch has been found in *Hfm* heterozygote (±) mutant embryos at E9.5. The *Hfm* locus has been mapped to mouse chromosome 10 by *in situ* hybridization (45). This region of mouse chromosome 10 is similar to parts of human chromosome 6q (46), making genes in this region potential candidate genes that may influence the occurrence of hemifacial microsomia or microtia in humans.

The *Far* (first arch malformation) mutation arose in the BALB/c strain of mice, with its phenotype inherited in an autosomal recessive manner (47–49). Interestingly, the region of human chromosome 2q24–q32 is similar to the region of mouse chromosome 2 where *Far* maps (50). One should then consider human chromosome 2q24–q32 as another potential region relevant to branchial arch disorders in humans. The phenotype of affected pups includes extensive bony defects of the face and skull, a cleft secondary palate, and early death within 24 h of birth. Most of the abnormalities occur in skeleton derived from the first branchial arch and most of the bony derivatives of the first arch are abnormal in the mutant.

The expressivity of this mutation can vary depending on other genetic factors in the same organism, particularly when *Far* is carried on the ICR/Bc strain genome (51). The hemifacial deficiency [38% of heterozygous (+/*Far*) animals] attributed to premature synostosis of the maxilla and pre-maxilla, is observable on day 16 of gestation. Additionally, 20% of (+/*Far*) heterozygotes in the ICR/Bc strain have cleft palate and die at birth. Most +/*Far* in both the BALB/c and ICR/Bc strains also have bilateral splitting of the maxillary branch of the trigeminal nerve. Homozygous (*Far*/*Far*) mice of both the BALB/c and ICR/Bc backgrounds have a syndrome of severe bilateral deficiency of the derivatives of the maxillary prominence. In human pedigrees, where the equivalents of the dominance modifiers in BALB/c and ICR/Bc would segregate within families, it would be difficult to recognize that sporadic hemifacial deficiency and severe bilateral maxillary deficiency were due to the same gene. These findings in the *Far* mutant would suggest that human bilateral and unilateral abnormalities of tissue derived from the first branchial arch should be analyzed with the awareness that, in mice at least, the two kinds of anomaly are due to the same mutant gene.

Clinical utility or implications

Dividing the discussion into separate sections on environmental and genetic factors suggests that they are separate, and that some cases of OAVS may be due to one or the either. Currently, there is an appreciation that normal and abnormal growth and development does not happen as a result of only environmental or only genetic factors. Variation in the response of individuals to an environmental factor may be in part due to variation in the genomes of the individuals, or variation in the genomes of individuals may result in varying susceptibilities to 'spontaneous' or teratogen

associated hemorrhage or other disruption of the developmental field. Thus, the clinician should exercise caution about making sweeping statements about etiology when thinking about normal and abnormal growth and development, and discussing it with patients and or their families.

Future research into this area needs to refine the definition of minimal diagnostic criteria which may only be some relatively mild change in external ear shape or facial asymmetry. Essentially, all patients have some degree of facial asymmetry. However, there is little objective evaluation of what is the 'normal' range of facial asymmetry, or rational basis for classifying a patient with facial asymmetry. Systematic analysis of facial morphology, including symmetry, will increase our understanding of what might be and not be considered normal variation in our general clinic population as well as in patients with developing anomalies. These studies may employ not only the standard anthropometric measurements taken by tape and caliper, but also the ever expanding field of three-dimensional imaging including the facial surface. As these new technologies advance it is imperative that new clinical 'analyses' be developed based upon population specific data.

An appreciation of the heterogeneity of facial asymmetry and the variability of associated cranial and extracranial anomalies should compel the clinician to look beyond the occlusal plane or the lower face to see if other cranial structures are affected, or if there is a medical history for extracranial anomalies that may be significant. Likewise if the clinician notices asymmetry of external ear development, a focused evaluation of facial symmetry and the level of the occlusal plane should be undertaken.

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