

Revisiting the Etiology of Hemifacial Microsomia

Retomando la etiología de la microsomía hemifacial

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ABSTRACT

Background: Hemifacial microsomia (HM) is one of the most common congenital facial malformations of newborns worldwide. Despite its prevalence, little is known about its etiology. Features of HM vary among different reports in the literature, affecting ears, mouth, and mandible on one or both sides. **Purpose and Methods:** We performed a systematic literature review to determine if there is new evidence regarding the pathological origins of HM. During a seven-month period (September 2010-April 2011) an exhaustive electronic database search was constructed. An inclusion criterion, which set the specific parameters of the electronic database search for this review, was implemented using a number of built-in search tools. **Results:** A total of 1,250 published reports were displayed upon entry of the Boolean phrase "etiology AND hemifacial microsomia." Of these papers, all of the publications selected for by the inclusion criterion had been published within the last ten years. Concomitantly, with regards to etiologic origins, selection of a specific paper had to convey theories or experimental approaches of which had not been published as the main focus of a report more than three times in all with regards to previous documented literature with hemifacial microsomia as its basis. This final inclusion criterion left only eight studies eligible for this review. Reports included the suggestion of an etiologic role of growth hormone deficiency, fluoxetine ingestion, *SALL4* expression, *BAPX1* expression, and trisomy of chromosome 10. It appears that both genetic and environmental factors play a role in the etiology of HM. These factors include gene mutations, variation in serotonin receptor binding, growth hormone imbalances, and chromosomal abnormalities. Future studies in humans should determine the frequency of etiologic coding mutations in *SALL4*, *BAPX1*, and trisomy 10 in HM cases.

KEYWORDS

Congenital malformation; etiology; hemifacial microsomia; manifestation

THEMATIC FIELDS

Congenital abnormalities; craniofacial abnormalities

RESUMEN

Antecedentes: la microsomía hemifacial (MH) es una de las malformaciones faciales congénitas más frecuentes en recién nacidos. A pesar de su prevalencia, poco se sabe sobre su etiología. Las características de la MH varían en los diferentes reportes de la literatura; afecta oídos, boca y mandíbula, uni o bilateralmente. **Propósito y métodos:** se llevó a cabo una revisión sistemática de la literatura para determinar si hay nueva evidencia sobre el origen patológico de la MH. Durante siete meses (septiembre de 2010-abril de 2011) se realizó una búsqueda exhaustiva en bases de datos electrónicas. Un criterio de inclusión que determinó los parámetros específicos de la búsqueda se implementó usando un número de herramientas de búsqueda. **Resultados:** la búsqueda booleana ("etiology AND hemifacial microsomia") arrojó un total de 1250 publicaciones. Se seleccionaron reportes publicados en los últimos diez años. Asimismo, con respecto a la etiología, los artículos debían incluir teorías o experimentos que no se hubieran publicado como asunto principal más de tres veces con la MH como base. Este criterio final de inclusión dejó solamente ocho estudios elegibles para la revisión. Los reportes sugieren que una deficiencia en la hormona del crecimiento, ingestión de fluoxetina, expresión de *SALL4*, expresión de *BAPX1* y trisomía del cromosoma 10 como factores etiológicos. Parece que factores genéticos y ambientales cumplen un papel en la etiología de la MH. Estos factores incluyen mutaciones genéticas, variación en la unión del receptor de la serotonina, desbalances de la hormona del crecimiento y anomalías cromosómicas. Estudios futuros en humanos deberían determinar la frecuencia de mutaciones etiológicas en la codificación de *SALL4*, *BAPX1* y trisomía 10 en casos de MH.

PALABRAS CLAVE

Etiología; malformación congénita; manifestación; microsomía hemifacial

ÁREAS TEMÁTICAS

Anomalías craneofaciales; anomalías congénitas

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INTRODUCTION

Hemifacial microsomia, also known as oculo-auriculo-vertebral spectrum (OAVS), or expanded “Goldenhar Syndrome,” is the second most common craniofacial birth defect apparent in newborns. The syndrome tends to have a male preponderance. The right side of the face and/or body is more commonly and severely affected than the left side.

Currently, there is no reported primary cause that has been established through experimental investigation. Many studies have been undertaken in order to explain the mechanism behind hemifacial microsomia. Prominent theories range from deleterious genetic mutations (1), vascular disruption with expanding hematoma formation *in utero* (2), autosomal dominant inheritance (3), and first and second branchial arch malformation (4).

Hemifacial microsomia has a wide phenotypic variation and no uniform criterion for diagnosis exists. It is generally accepted that the spectrum includes some of the following abnormalities: ear malformations, micrognathia, epibulbar dermoids/lipodermoids and/or colobomas, and vertebral defects. The maxillary, temporal, and malar bones on the more severely involved side are somewhat reduced in size and flattened (5). Cervical vertebral fusions occur in 20 to 35% of cases, whereas platybasia and occipitalization of the atlas are found in about 30% (6).

The goal of this study was to assess the most recent etiological information of hemifacial microsomia to provide a summary to guide further investigation of a potential etiology of interest.

METHODS

Within the span of a seven-month period (September 2010 to April 2011) an exhaustive electronic database search was constructed. An inclusion criterion, which set the specific parameters of the electronic database search for this review, was implemented using a number of built-in search tools. The criterion, listed below, were decided upon after two months of searching various electronic databases via the University of Pittsburgh Health Sciences Library System, in order to narrow down the most recent, relevant information that has been presented or published within the last ten years regarding the etiology of hemifacial microsomia:

1. Authorized access to the online database via the University of Pittsburgh Health Sciences Library System.
2. Within the Document Search tab, under “Search for,” the Boolean keywords used were “hemifacial microsomia AND etiology” in “Article Title, Abstract, Keywords”.
3. Under the “Limit to” tab: Published “2001 to Present,” Document Type – All.
4. Subject Areas: Life Science, Physical Sciences, Health Sciences, Social Sciences & Humanities.

Upon completion of the search with each database, a total of 1250 published reports fit the criteria of the project. The only publications discerned out of this group in order for discussion of recent findings with regards to etiological origins had theories or experimental approaches of which had not been published more than three times in all of the previous documented literature with hemifacial microsomia as its basis. This final inclusion criterion left only eight studies eligible for this review.

RESULTS

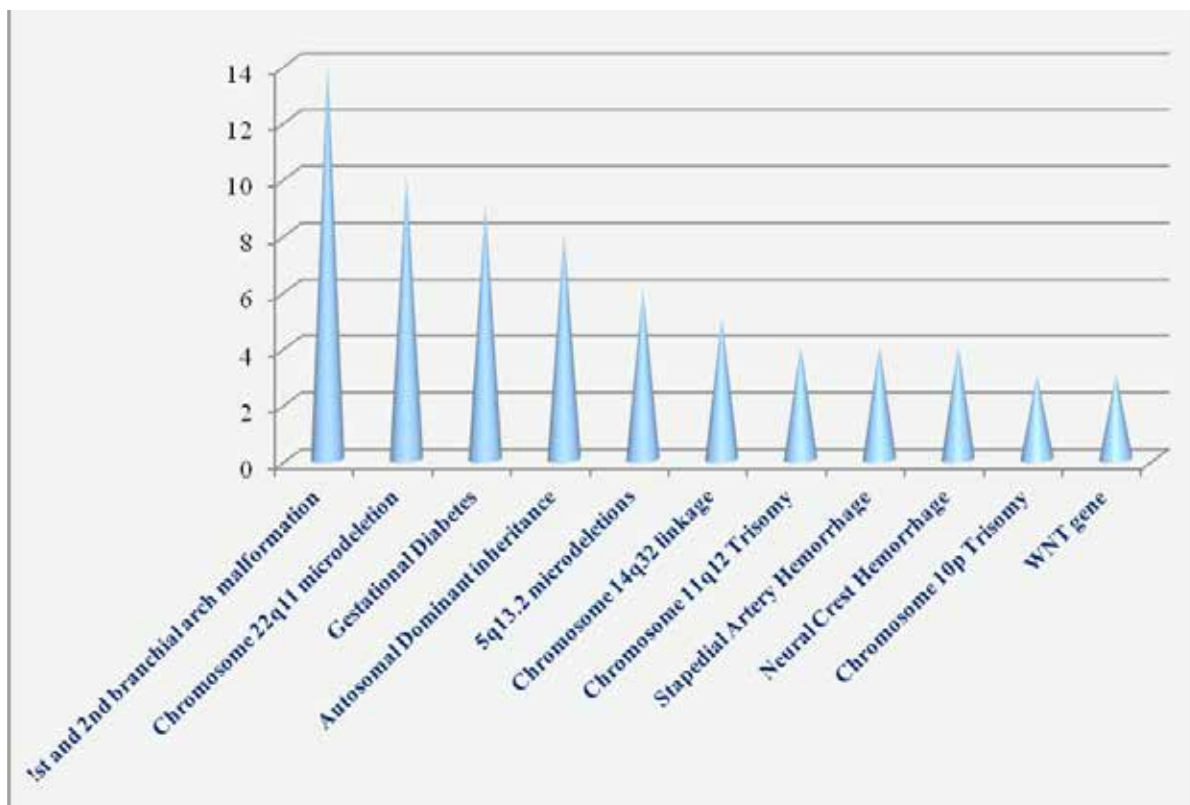
A total of 19 electronic or online databases were used in order to complete this review. The specific titles of each database searched are located in Table 1. Upon completion of the search, a total of 1250 published reports were displayed upon entry of the Boolean phrase “etiology AND hemifacial microsomia.” Table 1 displays the number of queries that were found for each database. Figure 1 displays the top ten etiological theories based on the number of publication sources that touted the specific theory as a cause for hemifacial microsomia. Of these papers, all of the publications selected for by the inclusion criterion had been published within the last ten years. Concomitantly, with regards to etiological origins, selection of a specific paper had to convey theories or experimental approaches of which had not been published as the main focus of a report more than three times in all with regards to previous documented literature with hemifacial microsomia as its basis. For example, a study validating the involvement of the stapedia artery as the impetus that causes facial malformations characterized as hemifacial microsomia would have already been previously presented due to the number of reports published by

Poswillo's group in the sixties and seventies that discussed the same theory. Therefore, this particular paper would not have been eligible to be included within this study. This final inclusion criterion left only eight studies eligible for this review. These studies are summarized in the Discussion section.

TABLE 1
 DATABASES SEARCHED AND QUERIES FOUND USING THE BOOLEAN PHRASE
 "ETIOLOGY AND HEMIFACIAL MICROSOMIA"

Database	Number of hits per database
PubMed/Medline	798
EMBASE	280
Ovid @ Books	108
Scopus	22
Web of Knowledge	17
Biosis Previews	10
Biomed Central	4
EBSCO Host	4
World Cat	3
Global Health (OVID)	2
Access Medicine	1
Proquest Dissertations	1
EMTALA	0
NLM Gateway Database	0
Proceedings	0
Clinicaltrials.gov	0
metaRegister of Controlled trials (mRCT)	0
WHO ICTRP	0
nyam.org	0
TOTAL	1250

FIGURE 1
TOP TEN ETIOLOGICAL THEORIES BASED ON THE NUMBER OF PUBLICATION SOURCES THAT TOUTED A SPECIFIC THEORY AS A CAUSE FOR HEMIFACIAL MICROSOMIA



DISCUSSION

Risk Factors

There are few published reports that take an experimental approach towards finding the causal indications that result in a young patient manifesting hemifacial microsomia. One study attempted to accomplish this with a massive retrospective case-control study, which tried to identify whether vasoactive exposures or vascular events during early pregnancy affect the risk of hemifacial microsomia (7). Cases with a diagnosis of hemifacial microsomia were identified at craniofacial centers in 26 cities across the United States and Canada, from 1996 to 2002. Mothers of 230 cases and 678 controls were interviewed about pregnancy events and exposures. Controls were matched to cases by age and pediatrician practice, where approximately 70% of controls were identified from the practice and the remainders were identified from a practice of similar size within the same zip code as the case's pediatrician. The controls were within two months of the case's age. Controls were ineligible if they were older than three years of age, had major malformations (chromosome abnormalities or Mendelian-inherited

disorders), endured isotretinoin exposure *in utero*, or were adopted. Mothers of cases and controls were interviewed over the phone by a study nurse and asked about demographic and reproductive factors, as well as pregnancy exposures and behaviors. The interview, according to the report, included specific questions about medication and illicit drug use, illnesses, cigarette smoking, and alcohol intake. Odds ratios (OR) were significantly increased for vasoactive medication use (OR 1.9 overall, 95% C.I. 1.2-2.9; OR, 4.2, 95% C.I. 2.0-8.9 among smokers), multiple gestations (OR 10.5, 95% C.I. 4.2-26.2), and diabetes (OR 6.0, 95% C.I. 2.5-14.3). The study reported that heavy alcohol intake and vaginal bleeding during the second trimester of pregnancy were associated with increased risks, but these associations are unstable due to the small numbers the estimates were based upon. There were no associations observed for cigarette smoking without vasoactive medication use, hypertension, and vaginal bleeding in the first trimester. The authors stated that the increased risks of hemifacial microsomia

associated with vasoactive medication use, multiple gestations, diabetes, and second trimester vaginal bleeding appear collectively to support the hypothesis that vascular disruption is one etiology for hemifacial microsomia, because each of these factors is related to effects on blood vessels.

The same group published a second report where other risk factors were analyzed in accordance with the retrospective case-control study that they conducted between 1996 and 2002. Demographic variables, such as ethnic background, socioeconomic status, maternal age, family income, and maternal marital status were examined. Reproductive factors such as birth weight, sex, family history of birth defects, and plurality (singleton versus multiple) were assessed as well (8). Additional factors examined were maternal years of education, pre-pregnancy height and weight, whether the pregnancy was planned, the date when the mother first suspected to be pregnant, vaginal bleeding, and the number of outcomes of previous pregnancies. There were a total of 239 cases and 854 controls interviewed for this study. According to the report, the odds of hemifacial microsomia increased with decreasing birth weight, male sex, and a family history of hemifacial microsomia. There was a decreased risk for African American mothers and an increased risk estimate for Native American mothers. There was no reported associated risk for maternal age and education. Low annual family income (<\$25,000) was associated with an approximate doubling in risk. Single mothers who were no longer with their partners and reported being single at the beginning of their pregnancy had a reduced risk estimate. A body mass index of less than 18 kg/m², suspicion of pregnancy after the ninth week, a previous spontaneous abortion, and a previous termination of pregnancy resulted independently with an increased hemifacial microsomia risk. Unplanned pregnancy and multiparity were not associated with an increased risk of hemifacial microsomia. The odds of vaginal bleeding in the fourth or fifth month of pregnancy were approximately ten times greater for hemifacial microsomia expectant mothers. The odds ratio for previous stillbirth was elevated but not statistically significant.

The theory of vascular injury, primarily to the stapled artery, is one that has held weight throughout the years. There have been few studies, however, that take a look at exactly how and/or why the vascular injuries occur in the first place, which makes this case-control reports by Werler et al. unique in its own right. The sample size (230 cases and 678 controls)

brings strength to the study, as well as the number of locations. The period of time in which the study was conducted, six years, seems like an adequate enough time to conduct the study considering the number of cases included. A longer term may reaffirm the results found, however, and increase the validity of the study. The authors stated that they “relied on the diagnostic ability of participating craniofacial specialists for case reporting and then reviewed craniofacial center records to confirm diagnoses reported at the time of ascertainment” (7,8). They themselves did not have a minimum criterion in which to qualify and accept a case into the study, such as the Orbital, Mandible, Ear, Nerves, and Soft Tissue (OMENS) scale, which would provide validation for inclusion based on a tangible measurement. A study nurse interview, unfortunately, is not an unbiased tool in which to ascertain aspects that hold a significant place within this study (though the same study nurse conducted every interview). Vocal tone could, and most likely did, play a role in the answers that some of the case and control mothers may have articulated, thereby potentially skewing the results of this study due to recall bias. A questionnaire, on paper mailed to each case and control subject with strict instructions and deadlines for return, or an online questionnaire program with the ability to be accessed by each participant within the study may have eliminated most of the “tone” bias that can accompany a verbal phone interview.

The vascular effects of gestational diabetes, most significantly when it is poorly controlled, have been documented over the years to have a strong association with hemifacial microsomia (9-11). The fact that the authors found an increased risk among expectant mothers who had this disease at one point during their pregnancy coincides with this trend. The buildup of glucose within the body causes many deleterious effects on the state of homeostasis, shunting away nutrients and enzymes that may be used in other key processes, such as eliminating reactive oxygen species. These entities can cause significant damage to the vasculature of both the mother and the fetus, at which point select vessel endothelium can rupture and produce an effusive hematoma *in utero*. Vasoactive medications, primarily vasoconstrictor agents, could have a deleterious effect on the fetus and cause a premature hematoma, especially due to the changes in physiology that most pregnant women endure (increased blood volume, higher mean arterial pressure, decreased blood viscosity, and transient increases in cardiac output). The increased risk among expectant mothers that have multiple maternities is an interesting

finding, and one that is corroborated by Lawson et al. (12). In this study, the prevalence of multiple births amongst a large number of affected individuals and their families was compared to the mean age-standardized twin maternity prevalence for England and Wales between 1975 and 1995 and the triplet maternity prevalence for the same two countries for the year 1995 (12). The prevalence of twin maternities amongst the affected individuals was 3.96% and amongst their siblings was 4.01% —both significantly larger than the 1.06% reported for the England and Wales twin maternities. As there were more twins amongst the affected individuals than in the general British population, the authors postulated that the etiology of hemifacial microsomia with associated microtia was more likely to occur during a pregnancy with the presence of co-twins or co-triplets (12). The Werler et al. reports seem to give this previous report credence, and can offer investigators an alternative path for research in order to find the reason for this association (7,8).

As evidenced by the number of studies discussed in this section, there is a clear lack of a definitive etiological cause to the disorder of hemifacial microsomia. The fact that it has a multifactorial etiology somewhat affected by the genetic makeup of each infant it manifests itself in provides a basis for the reasons behind the paucity of a defined etiology.

Genetics

The theories relayed by pioneers in the field in the late 1960s, such as Dr. Robert Gorlin, attempted to discuss the various forms in which the disease could manifest itself, as well as the heterogeneous origins that the syndrome could be caused by (13). Takahashi et al., among others, thought that the answer to the genetic puzzle lay in the expression of a specific group of homeobox genes called *Msx*. *Msx* appears to be critical for the differentiation of first branchial arch ectoderm-mesenchyme leading to various craniofacial structures (14). *Msx* genes are also strongly expressed in cephalic neural crest cells prior to the migration of the cells that contribute extensively to craniofacial development (1). Disruption of *Msx* in mice results in major abnormalities of first branchial arch derivatives (2). Thus, homeobox genes, especially of the *Msx* class, are candidate genes for oculo-auriculo-vertebral spectrum, particularly in familial cases (15). Mutations resulting in partial loss of function of these genes could explain incomplete penetrance and clinical variability occurring in individuals with differing genetic backgrounds (3). A case where three successive generations of a family had signs of hemifacial

microsomia suggests an autosomal dominant inheritance. All of the generations had one affected mother or father, indicating that the disease was transmitted in an autosomal dominant fashion (16). The variability in gene expression between the cases and the male-to-male transmission were also characteristic of a dominantly inherited trait (16). A segregation analysis found evidence for genetic transmission with an autosomal dominant inheritance (17). Others, however, have suggested that the syndrome itself is caused by an autosomal recessive inheritance pattern, noting the observation of affected siblings with normal parentage within the same immediate family (18).

Chromosomal abnormalities also appear to cause hemifacial microsomia. A partial 22q deletion in a patient with Goldenhar defect seems to support the concept of causal heterogeneity in this disorder (19). The list goes on in terms of causal chromosomal maladies manifesting phenotypes that come close to resembling hemifacial microsomia: dup(7q), X chromosome aneuploidy, del(5q), and trisomy 18, also known as Edwards Syndrome (20).

The *TCOF1* gene complex, which historically has been associated with Treacher-Collins syndrome, appears to be associated with hemifacial microsomia. Mutations in *TCOF1* were investigated in hemifacial microsomia patients exhibiting de novo microtia with meatal atresia (21). They examined five patients: four cases which exhibited multiple features of oculo-auriculo-vertebral spectrum and one case with Treacher-Collins syndrome. Upon PCR product analysis and sequencing, a number of interesting discoveries were reported. The group detected one typical oculo-auriculo-vertebral spectrum patient who had a missense mutation in exon 9 of the *TCOF1* gene and two silent mutations in exons 10 and 23. All four oculo-auriculo-vertebral spectrum patients had some sort of significant polymorphic finding with the *TCOF1* gene. Most specifically, a new missense mutation was observed in the complex (at position 362 where thymine is switched for adenine), a mutation that the authors believe could actually be potentially causative for typical hemifacial microsomia. This missense mutation is the first report of a *TCOF1* missense mutation occurring in an oculo-auriculo-vertebral spectrum patient. It appears that this particular gene is responsible for both Treacher-Collins syndrome and oculo-auriculo-vertebral spectrum but differs within their respective phenotypic expressions. Their first reason stems from the fact that most Treacher-Collins syndrome mutations are insertions or deletions of *TCOF1*, while this reported

mutation was a detected missense mutation that may have resulted in a variable expression of the gene and not complete premature termination. The group also acknowledged that other factors, such as maternal diabetes, alcohol, medications, and tobacco use could also play a secondary role in accordance to the mutated gene. The study did not examine those patients with bilateral Goldenhar syndrome. Despite this fact, the inclusion of *TCOF1* gene for consideration as a central, causal role is one that could prove worthwhile to researchers and physicians alike.

A young male patient with a tandem duplication of the short arm of one chromosome 10, with apparent breakpoints at p14 and p15 confirmed with FISH cytogenetic analysis, has been reported. The interesting notion is that the young patient showed a distinct trisomy of the tenth chromosome, but did not show any of the typical features that a patient with trisomy 10p would typically display (low birth weight, developmental delay, ear abnormalities, micrognathia, dolicocephaly, microcephaly, hypotonia, renal and cardiac abnormalities) (22). Also, since the parental karyotypes were normal, the patient's trisomy could be classified as "de novo" —a very rare occurrence when dealing with reported cases of trisomy 10p (23). A novel heterozygous nonsense mutation occurred in the *SALL4* gene complex of all affected members of a given family. All affected had variable clinical features, though all somewhat consistent with hemifacial microsomia. However, this study failed to establish a common genotype-phenotype effect that consistently presented in all of the subjects, likely due to the fact that other members had other syndromes affecting them. These included Duane anomaly and Okinohiro Syndrome (24). Another suggested mechanism is that allelic expression imbalance of *BAPX1* predisposes patients to oculo-auriculo-vertebral spectrum (25). This study's hypothesis is based on two assumptions: that these imbalances are only found in patients and their relatives and that one of the patient's disease occurred *de novo* —therefore reflecting the traditional multifactorial nature of the disease (25). *BAPX1* expression in the first branchial arch marks a potential deleterious mechanism that can lead to oculo-auriculo-vertebral spectrum (25).

Vascular Injury

D.E. Poswillo, a researcher out of London, England, was one of the first prominent voices to separate from the contingency of researchers who believed that there is a causal genetic component to the disease. Poswillo claimed that the disorder's frequent occurrence on

one side of the face led to suggestion of interference with vascular supply and focal hemorrhage in the developing first and second branchial arch region. Between 1973 and 1975, Poswillo proposed that the pathogenetic makeup of hemifacial microsomia was based on an embryonic hematoma formation arising from the anastomosis that precedes the formation of the stapedia artery (26,27). The severity, variation, and heterogeneity of the symptoms of hemifacial microsomia were a direct result of the size and amount of hematoma collection and expansion, where small hematomas cause less damage than their larger counterparts with regard to branchial arch growth.

Two cases of hemifacial microsomia where there was evidence of carotid artery occlusion (28) and a case where the subject lacked an internal carotid artery and showed subsequent facial defects and unilateral hydranencephaly (29) have been reported. Despite many studies extolling this particular theory, many other papers have attempted to refute this line of thinking, stating that the occurrence of one or two specific abnormalities eliminates the consistency that forms the essence of the definition of a "syndrome." The appearance of preauricular tags in some of an affected person's relatives instead of a consistent set of symptoms makes the vascular injury theory hard to substantiate (30). It is suggested that it would be increasingly difficult to explain varying appearances (not expressions of the same phenotype) between members of a family with only vascular disturbance as the primary basis.

Teratologic Insult

Several teratogenic agents have produced hemifacial microsomia (6). Expectant mothers exposed to thalidomide, primidone, and retinoic acids have all been documented to cause facial congenital malformations amongst their respective newborns. Earlier, a series of experiments regarding amniotic band disruption secondary to intrauterine compression in rats that seemed to manifest hemifacial microsomia symptoms have been reported. Secondary to oligohydramnios, this feature could cause an embryonic hematoma and subsequent damage (31). It seems that this particular theory could coincide partially with Poswillo's proposed vascular injury insult.

Other Causes

Lin et al. in 1998 had yet another interesting take on the etiology of this disorder. He postulated that there is a midline field defect during blastogenesis within the embryo. They go on to claim that Goldenhar complex,

or hemifacial microsomia, may be a marker for inflammation and defects of midline development rather than just a disorder mainly of the head and neck (32).

An expectant mother with a history of fluoxetine ingestion and no previous family history of hemifacial microsomia had a male child born with oculo-auriculo-vertebral syndrome. Fluoxetine, a common substance used in anti-depressant medication, has not been linked to significant fetal malformations before in the past. It was suggested that serotonin's role in the primitive streak may be essential during gastrulation. Uptake from the floor plate of the developing neural tube, as well as a role in facilitating cellular migration that is important in neural crest formation, palatal shelf elevation, tooth bud invagination, and dental papilla condensation, makes serotonin a significant player in early fetal facial development (33). Serotonin binding proteins, expressed in most craniofacial regions at critical times during craniofacial development, may have a buffering capacity that maintains adequate serotonin tissue concentrations over a wide range of serum concentrations. Selective serotonin reuptake inhibitors, according to Farra's group, may create a serotonin receptor suppressive state *in utero*, leading to aberrant clinical manifestations of craniofacial development (33). This study provides an interesting take on how selective serotonin reuptake inhibitors could provide an exogenous mechanism that could produce the features of oculo-auriculo-vertebral spectrum. Further studies could be conducted in order to investigate this new avenue of thinking.

Growth Hormone Deficiency

A young patient was diagnosed with hemifacial microsomia due to its clinical presentation: facial asymmetry, right hemifacial microsomia, right microtia, right external auditory canal atresia, lumbar scoliosis, bilateral clinodactyly, and a pansystolic murmur (34). MRI studies displayed both mild cervical lordosis and right-angled scoliosis, along with cranial lacunar infarcts within the left thalamus. Originally admitted to the hospital because of "short stature," a complete hematological workup revealed that the patient had been suffering from a growth hormone (GH) deficiency. The patient's GH responses to L-dopa and insulin stimulation tests were 12 ng/mL and 6.8 ng/mL, respectively [normal levels (normal = N) are >10 ng/mL] (34). A secondary test was given on a follow up two years after the initial analysis to confirm the diagnosis. A parachute mitral valve was also reported in this case's findings. The patient had undergone a surgical correction of an aortic stenosis blockage at the age of

eight (the study was completed when the patient was approximately ten years of age). The patient also had a high lipoprotein-a level, which may have contributed to cerebral thrombosis.

The association of growth hormone deficiency with hemifacial microsomia is a relatively nascent discovery that has not been explored much. The fact that a lack of growth hormone has rarely been documented as a manifestation of hemifacial microsomia begs into question the validity of its inclusion among "causal" links. Yusofglu et al., to their credit, did not seem to try and convey the notion that the young patient's lack of growth hormone held any causal significance to his other malformations. However, the study's authors documented both the growth hormone deficiency and the parachute mitral valve as additional features in accordance with the other aspects of the syndrome, implying that these two traits may be an evolving part of the disease rather than random anomalies (34).

There is only one other published report that deals with this particular mechanism (35). The authors reported a similar case documenting a 10 year-old Japanese hemifacial microsomia patient who displayed microtia, left accessory auricle, left mandibular hypoplasia, and left epibulbar dermoids. He had idiopathic GH deficiency and was treated with growth hormone, which was effective. The patient documented by Yusofglu et al. displayed a similar need for growth hormone treatment, according to the report (34). The patient's vertebral fusion defects, however, prevented them from administering therapy due to fear of subsequent scoliosis progression. There is no mention of a prolapsed mitral valve in the 1993 case report. The thalamic lacunar infarcts, according to the authors, may be a side effect from the corrective atrial stenosis surgery that the patient underwent as an 8 year old, and is not a relevant finding in terms of oculo-auriculo-vertebral spectrum.

Yusofglu and his team did not discern any definitive stance about their findings in terms of cause. They stated that the growth hormone abnormality could be due to chance or be a rare finding in this syndrome (34). Despite their hesitance, the need for further studies is apparent due to this study. The effect of hormonal imbalance, both in the fetus and expectant mother, has not been explored in a rigorous fashion regarding the disease of hemifacial microsomia. Though the effects that seem to cause the damage occur before major hormones are created *in utero* and play any sort of significant role within the fetus

[this particular report states that intrauterine injury/insult that could result in the features for hemifacial microsomia are believed to occur within 30 to 45 days of gestation (34)], it still offers a new avenue for research. What hormones are consistently deficient in hemifacial microsomia patients? Is there a delay in the production of hormones during gestation that could affect facial development weeks down the line? What if the expectant mother has growth hormone deficiency—are her chances of having a child stricken with oculo-auriculo-vertebral spectrum greater than normal? Future studies can attempt to discern any relevant correlations and associations that may lie within the hormonal makeup of both the fetus and pregnant mother that could possibly shed some light towards a relevant etiological hypothesis.

CONCLUSION

In conclusion, there seems to be a myriad of relevant studies being undertaken by experts within the field that primarily focus on the etiological cause of hemifacial microsomia. These studies, conducted within the last 10 years, are prime examples of the steps that researchers and clinicians are taking in order to find the principal cause of the disorder. Despite the efforts of those discussed within this manuscript, the fact that only eight studies qualified for the study may cause consternation as to how valid a sole etiological theory may be with this disorder. One may argue that due to a dearth of new ideas to come to the forefront within the last ten years, that there may eventually be a loss of interest towards bolstering the evidence for a single cause and increased backing for those who are advocates for multiple etiological triggers. Further development of these ideas, as well as others, can allow the medical and dental community to understand this congenital facial malformation better, erect guidelines in order to prevent its occurrence, and establish a solid protocol for administration of proper treatment. Future studies probably need to include minimally affected families to address the potential heterogeneity of hemifacial microsomia (36). Advances in the area of temporomandibular joint development and its disorders may also impact the understanding of hemifacial microsomia development (37).

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