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Hemifacial microsomia: From gestation to childhood

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Abstract

Hemifacial microsomia (HFM) is a variable, complex malformation involving asymmetric hypoplasia of the face and ear. Little is known about risk factors for or consequences of HFM. Here we describe three studies that have been or are currently being conducted to further our understanding of this malformation. The first, completed, study examined whether HFM risk is related to maternal exposures that may affect blood flow. In that case-control study, interview data from 230 mothers of cases and 678 mothers of control children suggested that maternal use of vasoactive medications in the first trimester, particularly in combination with cigarette smoking, was associated with increased risks of HFM. The second study is currently underway, in which we are evaluating whether HFM risk is related to genetic variation in pathways associated with vasculogenesis and hemostasis, using DNA collected in the first study. The third, on-going, study follows children with HFM to identify psycho-social, cognitive, dental, and medical sequelae. When the children from the original case control study are 6 or 7 years of age, mothers and teachers complete self-administered questionnaires that cover a wide range of psycho-social development domains. Preliminary analyses of 115 case and 314 control children suggest children with HFM may have worse teacher-reported academic performance and possibly higher levels of internalizing behavior problems than control children. When data on the full study sample are available, further analyses will determine whether the preliminary findings remain and if they vary by HFM phenotype, parenting style, or indicators of social risk.

Keywords

Hemifacial microsomia; Pregnancy; Genetics; Psycho-social outcomes

Introduction

Hemifacial microsomia is a variable, complex malformation that is most strictly defined as asymmetric hypoplasia of the face and ear. However, the defect is best described in terms of its embryologic development -- that is hypoplasia of structures derived from the first and second branchial arches during the first six weeks of gestation (1,2). The tissues that are typically

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affected include the condyle and ramus of the mandible, zygomatic arch, malar bone, external ear, middle ear ossicles, temporal bone, and muscles of facial expression. HFM may involve all or some of these structures (1-3). In fact, HFM is most notable for its vast array of craniofacial and extra-craniofacial manifestations, including associated malformations of other branchial arch derivatives such as the eye, vertebrae, and upper heart, as well as malformations of non-arch derivatives, such as the kidneys (1,3). Further, the term hemifacial implies the defect is unilateral, but structures are often affected bilaterally, though to different degrees, giving the facies an asymmetric appearance. Unilateral microtia may represent a form of HFM (4). Other terms, such as first and second arch syndrome, oculoauricular vertebral dysplasia, facioauricular vertebral spectrum, and Goldenhar syndrome, have been applied to HFM assuming different etiologies for cases with or without epibulbar dermoid and/or vertebral anomalies. However, it is now understood that these various combinations of eye and vertebral anomalies with HFM represent gradations in the severity of a similar morphogenic error (3).

There is evidence that genetics play a role in non-Mendelian-inherited HFM. Positive family history has been documented in a proportion of cases (5-10). Concordance has been reported for both monozygotic and dizygotic twins, but the high level of discordance in monozygotic twins suggests that both genetic and environmental factors are important (5,9-18). Based on families with inherited forms of HFM, the patterns of occurrence of both HFM and isolated microtia have suggested that either an autosomal recessive or autosomal dominant inheritance pattern is likely, (5,9-12,19-30) with reduced penetrance (28,31). Nevertheless, the majority of cases occur with no noted family history of HFM. Animal studies have shown that HFM can be induced genetically through a mouse chromosome 10 mutation, although a gene has not yet been identified (32-34); and mice deficient for any of several genes in the endothelin pathway exhibit a hypoplastic mandible, middle ear aberrations, and facial nerve defects, all of which are characteristic of HFM (35).

The embryology of HFM was first described in 1845, and a vascular pathogenesis was postulated as long ago as 1949. In 1973, Poswillo published his landmark paper suggesting hematoma might be involved in the development of HFM in rodents and primates (36). Specifically, a hematoma at the site of the developing stapedial artery and mandibular hypoplasia were observed among the offspring of CS1 mice treated with triazene during gestation. A similar hemorrhagic pattern was observed among Macaca irus monkeys treated with thalidomide in pregnancy; minor developmental delays of the condyle and middle ear primordia were also observed. Clinical evidence has been reported as well, where carotid flow was observed to be diminished on the affected side of HFM cases (37). This experimental and clinical evidence has raised the possibility that HFM might result from a vascular disruption pathogenesis (37,38).

Hearing loss, mastication impairment, breathing problems, speech impediments, and sleep disorders can occur as part of HFM. To improve function and appearance, a range of corrective surgeries may be indicated. Treatments and procedures can occur over many years and undoubtedly are disruptive to both child and family. HFM may have long-term effects on psychological development and social well-being, due to unusual facial appearance, functional problems, and medical treatments.

In this paper, we describe a series of studies of HFM aimed at closing the many gaps in knowledge about risk factors for and sequelae of HFM. The hypothesis addressed in the first study was that HFM risk is related to maternal exposures that may affect blood flow. In the second study, we are evaluating whether HFM risk is related to genetic variation in pathways associated with vasculogenesis and hemostasis. The third on-going study follows children with HFM in early elementary school to identify psycho-social, cognitive, dental, and medical sequelae.

Materials and Methods

Pregnancy risk factor case-control study

This retrospective, 26-center study was conducted from 1996 to 2002. Study subjects came from all regions of the United States and from two regions in Canada. Children diagnosed by a craniofacial specialist with HFM, facial asymmetry, or Goldenhar syndrome were included as cases. Controls were identified from each case's pediatrician (or a similar practice), matched to cases by date of birth (+/- 2 months). The mothers of 93% of eligible cases and 92% of eligible controls participated in the study. Mothers of cases and controls were interviewed within three years of delivery by telephone about demographic and reproductive factors, illnesses, medication use, diet, and other exposures and behaviors. Standardized and detailed questions were asked about possible exposures, including type, timing, frequency, and amount. In addition, cytobrush buccal cell samples were collected and returned via mail by 60% of case and control families.

We examined exposures in the first trimester, defined as the interval from the last menstrual period through 12 weeks gestation with the exception of vaginal bleeding, which included the early second trimester as well. Vasoactive medications included pseudoephedrine, phenylpropanolamine, aspirin, and ibuprofen. Odds ratios were generated as estimates of relative risk, adjusting for maternal age, education, race, income, body mass index, multiple gestations, cigarette smoking, alcohol intake, diabetes, hypertension, vasoactive medication use, and vaginal bleeding.

Genetic risk factor study

This recently funded project will take advantage of the buccal cell samples that were obtained from study subjects and their families in the case-control study. DNA from these samples will be used to address the vascular disruption hypothesis of HFM etiology, specifically, by assessing whether HFM risk is associated with variation in candidate genes involved in vasculogenesis and hemostasis. A relatively novel case-parent triad hybrid approach will be implemented that incorporates data from 172 case-parent and 382 control-parent sets. As possible “exposures,” we are selecting tagged single nucleotide polymorphisms, or “tagSNPs,” that comprehensively characterize the variation in 19 candidate genes that are involved in the activities of retinoic acid, endothelin, and thrombin. Both retinoic acid and endothelin are necessary for the proper development and patterning of the ear and mandible, among other structures (35,39-45). They also are necessary for vasculogenesis (35,39-43) and contribute to the maintenance of hemostasis and vascular tone (45-52). Genes in the thrombin pathway that are related to regulation and signaling are of interest, because they are necessary, through the receptor, PAR-1, for vascular development (52-55).

Follow-up study of psycho-social outcomes

This is an on-going assessment of cases and controls who were interviewed for the case-control study. When each child is 6 to 7 years of age, his or her mother and teacher are sent a packet of questionnaires and testing instruments covering a wide range of psycho-social development domains (summarized in Table 1). In addition, the child's dentist is sent a questionnaire to assess overall dental health; occurrences of caries, missing teeth, and malocclusion; orthodontic consultation; physical limitations to treatment; and behavior problems.

Because data collection is on-going, we present preliminary findings from teacher reports of child's behavior and competence on the subset of the study population that has participated thus far. Teacher reports of child psychological and social adjustment are thought to be less biased and are usually more predictive of future outcomes than parent reports (56,57). In contrast to most parents, teachers offer an adult's view of the child in relation to a relatively

large peer group of the same age. We used the well-known Teacher Report Form (TRF) (58-60) to obtain teacher's reports of children's academic performance, adaptive functioning, and behavioral/emotional problems. Teachers rate the children's academic performance in each subject on a five-point scale ranging from 1 (far below grade level) to 5 (far above grade level). To assess adaptive functioning, teachers use a seven-point scale to compare the child to typical pupils regarding how hard he/she is working, how appropriately he/she is behaving, how much he/she is learning, and how happy he/she is. Finally, teachers use a 3-point scale ("not true" to "often true") to rate the frequency of over 100 observed behavior/emotional problems (e.g., tantrums, noncompliance, anxiety) that are summarized by two broad scales: an *externalizing* scale that refers to inattentive/hyperactive and/or disruptive behavior problems and an *internalizing* scale that refers to shy, withdrawn or anxious/depressed behaviors.

In addition to the TRF, teachers used the *Social Competence Scale - Teacher Version* - a 25-item measure that focuses on children's prosocial behaviors and skills in emotional self-regulation (58). Each item describes a skill or prosocial behavior that a child may display at school, to which the teacher responds by indicating on a five-point scale how well each statement describes a particular child ("not at all" to "very well").

Each of the three studies were approved for human subjects research at participating institutions. Informed consent was obtained from study subjects.

For all measures, mean scores were calculated and compared between cases and controls, after adjustment for sex, birth year (continuous), maternal years of education (<12 years, 12 years, some college, 4-year degree, graduate school), race/ethnicity (White/non-Hispanic, White/Hispanic, African-American, Asian/Pacific-Islander, Native American, other), and region (northeast, mid-atlantic, midwest, south, west coast).

Results

Pregnancy risk factor case-control study

There were 230 cases and 678 controls, with an approximate 3:1 match for controls to cases. The patterns of demographic and reproductive factors for HFM (Table 2) have previously been described (61). Case mothers had similar ages and years of education, but had lower family incomes. Case mothers were also more often Native American and Hispanic, and were less often African American. Cases were more often male and twins.

Distributions of vasoactive exposures are shown in Table 3. Of the vasoactive medications, first trimester use of pseudoephedrine, phenylpropanolamine, aspirin, or ibuprofen was reported by more case than control mothers, but only pseudoephedrine use was independently associated with an increased risk of HFM after adjustment for other vasoactive exposures and demographic factors. The multivariate-adjusted odds ratio for smoking ≥10 cigarettes/day was compatible with no association, but smoking between one and 10 cigarettes/day was associated with a 2.3-fold increased risk. Alcohol drinkers of three drinks or more per day on three or more days per week had an increased risk of HFM (odds ratio=6.2; 95% confidence interval, 1.3-29.2) as compared with nondrinkers. Other possible vascular events -- multiple gestation, diabetes, and second trimester vaginal bleeding -- were associated with increased odds ratios, while hypertension and first trimester vaginal bleeding were not.

Pseudoephedrine, phenylpropanolamine, aspirin, and ibuprofen are typically taken episodically, while most women who smoke cigarettes do so on a daily basis. We therefore, looked at the combination of these exposures. The multivariate-adjusted odds ratio for women who both smoked and took vasoactive medications in the first trimester was increased 4.2-fold (data not shown) (61).

Follow-up study of psycho-social outcomes: Preliminary findings

We examined data reported by teachers on 115 case and 314 control children, representing approximately 70% of the study population. Mean scores for social competency, working hard, behaving appropriately, and externalizing behavior problems were similar for case and control children, after adjustment for sex, birth year, maternal years of education, and race/ethnicity. Similarly adjusted mean scores for learning and academic performance were lower for cases. Also, the adjusted mean score for internalizing behavior problems was higher (worse) for case children, but was not statistically significant (Table 4).

Discussion

Findings from this series of studies on HFM are still emerging, but thus far the results of the original case-control study are consistent with the vascular disruption hypothesis. Maternal use of vasoactive medications in the first trimester, particularly in combination with cigarette smoking, was associated with increased risks of HFM. Other associations with HFM that might represent vascular events include multiple gestations, diabetes, 2nd trimester bleeding, and heavy alcohol consumption. Vascular effects have been linked to each of these events and exposures both within the pregnancy period (62-66) and outside of pregnancy (67,68). However, some of the observed increased risks for HFM could also result from other pathogenetic processes such as neural crest cell apoptosis (69) or processes involving oxygen free-radical generation (65,70). A more detailed discussion of these results has been previously published (61). Findings from our recently begun study of genetic variation in hemostasis and vasculogenesis will be informative with regard to the vascular disruption hypothesis.

Together, the completed and ongoing risk factor studies should fill an important gap regarding the vascular hypothesis of HFM, because previous studies of possible risk factors for HFM were limited to case-series and lacked information on most vasoactive events and exposures. Among the various exposures we evaluated, multiple gestations and diabetes have been studied by other investigators, and our positive findings are consistent with their reports (71-73).

The pregnancy risk factor case-control study of HFM is the largest to date and the only one in which exposure data were collected directly from mothers. However, maternal interviews were conducted on average 17 months after the first trimester of pregnancy, which is likely to have reduced recall accuracy. If the degree of inaccuracy of reported exposures was similar in cases and controls, odds ratio estimate may have been underestimated. If the accuracy of reported exposures was different for case and control mothers, odds ratio estimates may have been biased in either direction. A further limitation is that inclusion of milder HFM cases may be incomplete due to the study's requirement that cases must have been seen at a craniofacial center. In addition, while the number of HFM cases was sufficient for identifying pregnancy risk factors, the sample size with buccal swabs is smaller, potentially limiting the statistical power to detect associations with genetic variants, particularly those that are less prevalent. The amount of DNA collected by buccal swab is also small, possibly limiting the number of genetic variants that can be studied. Nevertheless, this will be the first non-pedigree-based study of its size to explore genetic risk factors for HFM.

The ongoing follow-up study will provide data on a large range of neurobehavioral and other outcomes in early elementary school-aged children, including quality of life; behavior, adaptive functioning, and social competence; cognition; dental health; and medical and surgical treatments. Preliminary data on a sub-set of the study population suggest that children with HFM may have worse teacher-reported academic performance and higher levels of internalizing behavior problems than children unaffected by craniofacial conditions. If these associations remain in the full data set, further analyses will determine whether they vary by HFM phenotype, parenting style, or indicators of social risk (e.g., level of education or income).

In addition, neuropsychological development may be more directly compromised by underlying major or minor CNS malformations associated with HFM (74).

Other studies that considered children with a range of craniofacial disorders grouped together suggested that as compared with “typical” children, affected children are more inhibited, depressed, anxious, and introverted, and less socially adept (75-77), however children with HFM made up a minority of these case series. The relation between facial symmetry and psychosocial adjustment has been evaluated in a group of 30 children with a variety of craniofacial anomalies, including 11 children with HFM (78). In comparing children with “symmetric” and “asymmetric” craniofacial conditions, emotional development and social competence appeared to be normal for this small sample, but approximately one third of the HFM cases had scores that suggested clinically significant levels of behavior problems. One in five had scores that suggested depression. A small study of 6 twin pairs who were discordant for HFM, aged 9 to 15 years, suggested that on average, affected twins had worse behavior problems and lower general self-esteem than their unimpaired twins (79). No differences were found in social competence scores. Although limited to only six twin-pairs, inherent in the study of discordant twin pairs is control of potential confounding factors, such as age, socioeconomic status, and parents.

Given the limitations of previous studies on psychosocial outcomes in children with HFM, the on-going follow-up study should offer important new information The large study population, with participation expected of over 200 children with HFM and 400 control children, allows psycho-social and cognitive outcomes to be examined within subgroups according to severity of HFM and presence and type of associated malformations. Unfortunately, standardized data are not available on craniofacial or CNS morphology, or on speech and hearing function, which could impact psychosocial and cognitive outcomes and may even account for the preliminary findings reported here.

Hemifacial microsomia is estimated to occur in 1 of 3500 births, yet there has been little research on its risk factors and sequelae. Fortunately, starting with the original case-control study, we are beginning to fill gaps in research. That study, and the subsequent genetic and follow-up studies, are each groundbreaking in terms of their multi-disciplinary approach and their potential impact on affected families.

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Table 1

Psychosocial domains and measures collected in the HFM Follow-up Study

Domain	Measure	Respondent	# Items
Parent-reported stress in relation to child and family	Parenting Stress Index (PSI) Parent Domain	Parent	Approximately 50 items
Child behavioral adjustment	Child Behavior Checklist (CBCL)	Parent	112
	Teacher Report Form (TRF)*	Teacher	113
	Parenting Stress Index—Child Domain	Parent	Approximately 50 items
Child quality of life and adaptive functioning	PedsQL 4.0 (Parent report version)	Parent (parent version for children 5-7 or 8-12)	23
	PedsQL 4.0 (Child report version)	Child (version for ages 5-7 or ages 8-12)	23
Child social competence	Social Competence Scale - Parent Version	Parent	12
	Social Competence Scale - Teacher Version	Teacher	25
	TRF Social Competence items	Teacher	5 rating scales
Child's peer popularity	Teacher social acceptance ranking of all children in class	Teacher	Ranking among peers of same sex
Child neurocognitive status	Peabody Picture Vocabulary Test-III (PPVT-III)*	Teacher administration to child	Basal –ceiling requires 10-15 minutes
	Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)*	Teacher administration to child	Maximum of 24 items (10-15 minutes basal to ceiling)
	TRF academic performance ratings	Teacher	6 ratings by academic subject area

Table 2

Demographic characteristics and risk of HFM[#]

Characteristics	Percent of cases n=230	Percent of controls n=678	MVOR[*] 95% CI[*]
Age (years)			
<20	8	8	0.70.3-1.6
20-24	19	18	0.80.4-1.5
25-29	26	29	0.90.5-1.5
30-34	32	30	1.00.6-1.7
≥35	15	15	Ref.
Education (years)			
<12	21	15	1.00.5-2.0
12	22	23	1.10.7-2.0
13-15	24	22	1.40.9-2.4
≥16	33	40	Ref.
Family Income			
≤$15,000	14	10	1.30.6-2.8
$15,000-$25,000	17	11	1.70.9-3.5
$25,000-$35,000	10	12	0.90.5-1.9
$35,000-$65,000	21	28	1.00.6-1.6
>$65,000	28	30	Ref.
Refused/Unknown	11	8	1.50.7-3.3
Race			
Hispanic	26	16	2.21.3-3.7
Black	4	12	0.40.2-0.9
Asian	4	4	1.50.6-3.7
Native American	3	1	3.71.1-12.0
White	63	68	Ref.
Twin/triplet	9	1	11.04.4-27.3
Male	59	52	1.41.0-1.9

[#] Modified from (62).

[*] Multivariate odds ratio (MVOR) and confidence interval (CI) adjusted for all factors in tables 2 and 3.

Table 3

Vasoactive exposures and risk of HFM#

Exposure/event	Cases (%) n=230	Controls (%) n=678	MVOR*	95% CI*
Pseudoephedrine	18.7	12.1	2.0	(1.2-3.4)
Phenylpropanolamine	2.2	1.2	0.8	(0.2-3.2)
Aspirin	6.1	3.5	1.5	(0.7-3.4)
Ibuprofen	12.2	7.4	1.7	(0.9-3.0)
Cigarette Smoking- 1st trimester				
1-9/day	10.4	5.2	2.3	(1.2-4.4)
≥10/day	12.2	12.4	1.2	(0.7-2.1)
Alcohol drinking-1st trimester				
≤2 drinks/d or ≤2 drinking d/wk	35.2	40.1	0.8	(0.5-1.2)
≥3 drinks on ≥3 d/wk	1.7	0.4	6.2	(1.3-29.2)
Diabetes	7.8	1.5	6.0	(2.5-14.3)
Hypertension	3.5	2.4	1.2	(0.5-3.3)
Vaginal bleeding**				
1st trimester	16.1	13.0	1.0	(0.6-1.6)
2nd trimester	3.5	0.3	13.2	(2.3-75.8)

Modified from ref 62.

* Multivariate odds ratio (MVOR) and confidence interval (CI) adjusted for all factors in tables 2 and 3.

Table 4

Preliminary findings on teacher reports of childhood psycho-social factors in children with HFM

Problem	Domain	Measurement	Higher score is:	Unadjusted mean score		
				HFM n=115	Control N=314	MVDifference** (95% CI)
Behavior	Internalizing	Teacher Report Form	Worse	51.0*	48.3*	3.0 (0.9, 5.1)
	Externalizing	Teacher Report Form	Worse	48.9*	48.5*	1.0 (-1.0, 2.9)
Competency	Social	Social Competence Scale [a]	Better	2.7	2.9	0.0 (-0.3, 0.1)
Adaptive functioning	Academic Performance [b]	Teacher Report Form	Better	3.0	3.4	-0.3 (-0.4, -0.1)
	Working hard	Teacher Report Form	Better	4.5	4.8	-0.2 (-0.5, 0.1)
	Behaving appropriately	Teacher Report Form	Better	4.8	5.0	-0.1 (-0.4, 0.3)
	Learning	Teacher Report Form	Better	4.4	5.0	-0.4 (-0.8, -0.1)

[a] Social Competence Scale missing for 2 HFM and 3 control subjects.

[b] Academic Performance missing for 2 HFM and 3 control subjects.

* Unadjusted mean t-score.

** Multivariate adjustment, 95% confidence interval. Adjustment for sex, birth year, maternal education, race, region.