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Haemangiomas and associated congenital malformations in a large population-based sample of infants

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Summary

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Haemangiomas are common, benign, vascular tumours, observed in 4–12% of infants during the first year of life. Most cases progress without complication, yet a small proportion experience life-threatening complications. Concomitant congenital malformations have been reported in a small but significant proportion of haemangioma patients. This study aimed to describe haemangioma cases and to identify patterns of congenital malformations associated with these diagnoses in a large population. Diagnoses of haemangiomas and 21 congenital malformations were extracted from electronic medical records of 467 295 singleton infants born to US military families from 1998 to 2003. Cluster analysis was used to group cases according to these diagnoses. Multivariable logistic regression was used to further explore the associations of the 21 congenital malformations with the diagnosis of haemangioma and to assess the adjusted relationships between a number of characteristics of interest and diagnosis of haemangioma.

Clusters found to be associated with haemangioma were characterised by anomalies of the cervix, vagina, and external female genitalia, anophthalmia or microphthalmia, hydrocephalus without spina bifida, and reduction deformities of the brain. Logistic regression identified three congenital malformations significantly associated with haemangioma diagnosis: spina bifida without anencephalus, hydrocephalus without spina bifida, and anomalies of the cervix, vagina and external female genitalia. Characteristics significantly associated with haemangioma included female gender, preterm birth, white non-Hispanic race/ethnicity and increasing maternal age. This exploratory study identified a number of important associations between haemangiomas and congenital malformations that may provide insight into the pathogenesis of these disorders and have possible implications for clinical care.

Keywords: haemangioma, genital anomalies, CNS defects, congenital malformations, maternal age, preterm delivery.

Introduction

Haemangiomas are common, benign, vascular neoplasms, occurring in an estimated 4–12% of infants, either present at birth or appearing during the first year of life.^{1–3} Haemangiomas are generally characterised by rapid growth during the first months of life, followed by spontaneous slow regression; on an individual basis, however, their

course is unpredictable.⁴ A small percentage of cases experience life-altering or life-threatening complications and may require medical or surgical intervention.⁵ Demographic factors potentially associated with haemangiomas include female gender,^{3,4,6–9} Caucasian race,^{7–9} preterm birth and low birthweight,^{2,9–11} multiple gestation, and increasing maternal age.⁹

Single and multiple congenital malformations occurring in association with haemangiomas have been described in numerous studies.^{7,12–32} Various syndromes have been proposed when similar constellations of malformations have been observed in multiple haemangioma patients.^{18–20,22,26} The literature on these associations and syndromes is dominated by case reports and reviews. Lack of comparison groups and small sample sizes preclude evaluation of statistical associations in such studies. The existence of true associations is called into question by the fact that haemangiomas are relatively common and may be observed with concomitant malformations by chance alone.¹⁵

The Centers for Disease Control and Prevention have been actively monitoring and researching congenital malformations since 1967.³³ In addition, most states have established congenital malformation surveillance programmes.³⁴ However, these programmes do not include surveillance for infant neoplasms. In 1998, the US Department of Defense (DoD) established a surveillance programme for congenital malformations among military families.³⁵ Surveillance for infant neoplasms was added as a complementary component of this programme. These efforts have provided a data set with a natural comparison group and a sample size that far surpasses those that have been reported in the literature. Thus, these data present a unique opportunity to examine statistical associations between haemangiomas and congenital malformations, as well as to identify predisposing factors for haemangiomas.

Gaining a better understanding of the relationship between haemangiomas and congenital malformations would provide insight into the pathogenesis of these disorders. Furthermore, quantifying these relationships could have implications for clinical care if clinically apparent haemangiomas were quantitatively established as potential indicators of certain occult congenital malformations. The objectives of this study were to identify patterns of congenital malformations and characteristics associated with haemangiomas in infants born to US military families.

Methods

Data sources

The DoD Birth and Infant Health Registry provided the data for analyses.³⁵ This database captures all livebirths to military families, as well as health outcomes for all infants through the first year of life from three inde-

pendent military health data repositories. Electronic records of hospitalisations and outpatient care at military medical facilities are represented in the Standard Inpatient Data Record and the Standard Ambulatory Data Record systems respectively. Electronic records of DoD-financed hospitalisations and outpatient care at civilian medical facilities are represented in the Health Care Service Record, which is maintained by the DoD TRICARE health insurance programme. The database also contains demographic and service-related data for all parents who are military members, extracted from the Defense Enrollment Eligibility Reporting System and the Defense Manpower Data Center.

Validation methods

Validation of all cases in the surveillance system was not logistically feasible. Inpatient and outpatient records for a subset of congenital malformation cases in the electronic surveillance system were reviewed by experienced abstractors. In addition, active case ascertainment was performed to assess potential under-reporting, over-reporting or miscoding of congenital malformations in the electronic surveillance system. Experienced abstractors reviewed hospital and clinic logs to identify new diagnoses of congenital malformations. These data were compared with electronic surveillance data to verify diagnoses. Findings from these validation efforts were considered in interpretation of data and analyses. No validation of haemangioma cases has been performed.

Study population

The study population included 547 695 singleton infants born to DoD healthcare beneficiaries during 1998–2003. DoD healthcare beneficiaries are primarily active-duty military personnel and their families. During this time period, DoD-sponsored births took place in all 50 of the United States and the District of Columbia, as well as in 34 foreign countries.

Some variables in the data set were constructed such that infants with missing data were grouped with those in 'other' categories. For these variables, infants with missing data could not be differentiated from those in the 'other' categories. Because of the resulting difficulties in interpreting results regarding these categories, these infants, as well as those with any other missing data, were excluded from analyses.

Outcome measures

Outcomes of interest included haemangioma and congenital malformation diagnoses. All diagnoses were identified by the *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) system.³⁶ ICD-9-CM codes for haemangioma diagnosis include 228.0–228.09. ICD-9-CM codes for congenital malformation are within the range of 740.0–759.9. Diagnoses were identified in electronic records of medical visits during the first year of an infant's life.

Congenital malformations considered for inclusion in analyses were taken from the list of major malformations recommended for surveillance by the National Birth Defects Prevention Network (NBDPN).³⁷ This list was reduced by additional criteria. Congenital malformations for which a large proportion of diagnoses could not be validated in chart reviews were excluded; these included atrial septal defect (745.5), patent ductus arteriosus (747.0) and congenital hip dislocation (754.30, 754.31, 754.35). Congenital malformations known to be associated with low expected survivability were excluded because infants with these diagnoses were less likely to be diagnosed with haemangiomas; these included anencephalus (740.0–740.1), trisomy 13 (758.1) and trisomy 18 (758.2). All congenital malformations that occurred in fewer than five infants who also had haemangioma diagnoses were excluded. Additionally, infants diagnosed with tetralogy of Fallot (745.2) were coded with the specific malformations that defined the condition, ventricular septal defect (745.4) and pulmonary valve atresia/stenosis (746.01, 746.02). Three additional malformations not present in the NBDPN list, but identified in the literature as potentially associated with haemangiomas, were: reduction deformities of the brain (742.2), persistent fetal circulation (747.83), and anomalies of the cervix, vagina and external female genitalia (752.40, 752.41, 752.49).^{7,15,17,28,38} Twenty-one diagnoses made up the final list of congenital malformations included in analyses.

Clinical and parental characteristics

A number of clinical and parental characteristics were of interest as potentially associated with the occurrence of haemangiomas. Unless otherwise specified, parental characteristics refer to the parent identified as the infant's military sponsor in the personnel and medical records. Clinical characteristics included infant gender, infant birth status (full term, preterm), infant race/

ethnicity (white non-Hispanic, black/Hispanic/Asian; based on parent's race/ethnicity) and maternal age (<25 years, 25–34 years, ≥35 years). A number of other parental characteristics were included in analyses, primarily to adjust for possible differences in health care service utilisation. These included maternal marital status (married, unmarried), parent's branch of service (Army, Air Force, Navy, Marines), parent's rank (enlisted, officer) and parent's military occupation (combat specialist, health care specialist, other).

Statistical analyses

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA). Descriptive analyses were used to describe the distribution of the study population with respect to presence of haemangioma and the clinical and parental characteristics of interest. Regression diagnostics were used to screen for multicollinearity among the variables. Model goodness-of-fit was assessed using the Hosmer-Lemeshow test. Logistic regression was performed using the GENMOD procedure to assess the association of clinical and parental characteristics with haemangioma diagnosis, adjusting for potentially correlated outcomes among siblings.³⁹ Significance of variables was established at $P < 0.05$. Variables found not to be significantly associated with haemangioma in a saturated model were removed, and a final, reduced model was calculated. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable.

Patterns of congenital malformations occurring in association with haemangiomas were explored using cluster analysis. Infants were clustered according to the 21 congenital malformation variables. *K*-means clustering was performed with random selection of the initial seeds.⁴⁰ Multiple runs were performed, varying the number of clusters from 2 to 15, and with three different random seed initialisation values. For each random seed initialisation value, the cubic clustering criterion, pseudo-*F* statistic and total *R*-squared were plotted against the number of clusters. Local peaks of the cubic clustering criterion and the pseudo-*F* statistic, at reasonably high values of the total *R*-squared, the proportion of total variance in the data explained by the clustering, were used to identify optimal clustering solutions.⁴⁰ Three different solutions, one from each random seed initialisation value, were compared for consistency. Each solution was examined to identify the congenital

malformations that characterised each cluster. In each solution, one cluster, consisting primarily of infants without congenital malformation diagnoses, was designated as the reference cluster with which all other clusters in that solution were compared. The association of haemangiomas with each cluster relative to the reference cluster was assessed with ORs and *P*-values.

The association of congenital malformations with haemangiomas was further explored by logistic regression (GENMOD procedure), with haemangioma as the outcome variable and all of the congenital malformations included in the cluster analysis as independent variables. The model was adjusted for clinical and parental characteristics and potentially correlated outcomes among siblings.

Results

After exclusion of infants in 'unknown' or 'other/unknown' demographic categories, 467 295 infants remained in the sample for analyses. Alternative analyses demonstrated that excluding these infants did not substantially change any ORs for specific categories in logistic modelling.

The clinical and parental characteristics of infants with and without haemangiomas are reported in Table 1. Among the 467 295 infants in the sample, 5313 (1.1%) were diagnosed with haemangiomas during the first year of life. Compared with infants without haemangiomas, infants with haemangioma diagnoses were more likely to be female, preterm, of white non-Hispanic race/ethnicity, born to older

Table 1. Clinical and parental characteristics of singleton infants born to US military families, 1998–2003, and results of final logistic regression model

Variable	Infants without haemangioma diagnosis (<i>n</i> = 467 295) <i>n</i> (%)	Infants with haemangioma diagnosis (<i>n</i> = 5313) <i>n</i> (%)	AOR	[95% CI]
Gender				
Male	244 242 (52.9)	2161 (40.7)	1.00	Reference
Female	217 740 (47.1)	3152 (59.3)	1.65	[1.56, 1.74]
Birth status				
Full term	431 786 (93.5)	4791 (90.2)	1.00	Reference
Preterm	30 196 (6.5)	522 (9.8)	1.62	[1.48, 1.78]
Race/ethnicity				
Black, Hispanic or Asian	147 416 (31.9)	1178 (22.2)	1.00	Reference
White non-Hispanic	314 566 (68.1)	4135 (77.8)	1.59	[1.48, 1.70]
Maternal age (years)				
<25	205 729 (44.5)	2099 (39.5)	1.00	Reference
25–34	220 506 (47.7)	2705 (50.9)	1.12	[1.05, 1.19]
≥35	35 747 (7.7)	509 (9.6)	1.25	[1.12, 1.38]
Maternal marital status				
Married	435 014 (94.2)	5086 (95.7)	1.00	Reference
Single	26 968 (5.8)	227 (4.3)	0.85	[0.74, 0.97]
Parent's branch of service				
Army	175 435 (38.0)	1696 (31.9)	1.00	Reference
Air Force	117 050 (25.3)	1471 (27.7)	1.21	[1.12, 1.29]
Navy	115 256 (25.0)	1499 (28.2)	1.33	[1.24, 1.43]
Marines	54 241 (11.7)	647 (12.2)	1.22	[1.12, 1.34]
Parent's rank				
Enlisted	380 956 (82.5)	4159 (78.3)	1.00	Reference
Officer	81 026 (17.5)	1154 (21.7)	1.12	[1.05, 1.21]
Parent's military occupation ^a				
Combat specialist	102 908 (22.3)	1227 (23.1)		
Health care specialist	41 493 (9.0)	472 (8.9)		
Other	317 581 (68.7)	3614 (68.0)		

^aParent's military occupation was not included in the final model.

AOR, adjusted odds ratio; CI, confidence interval of odds ratio.

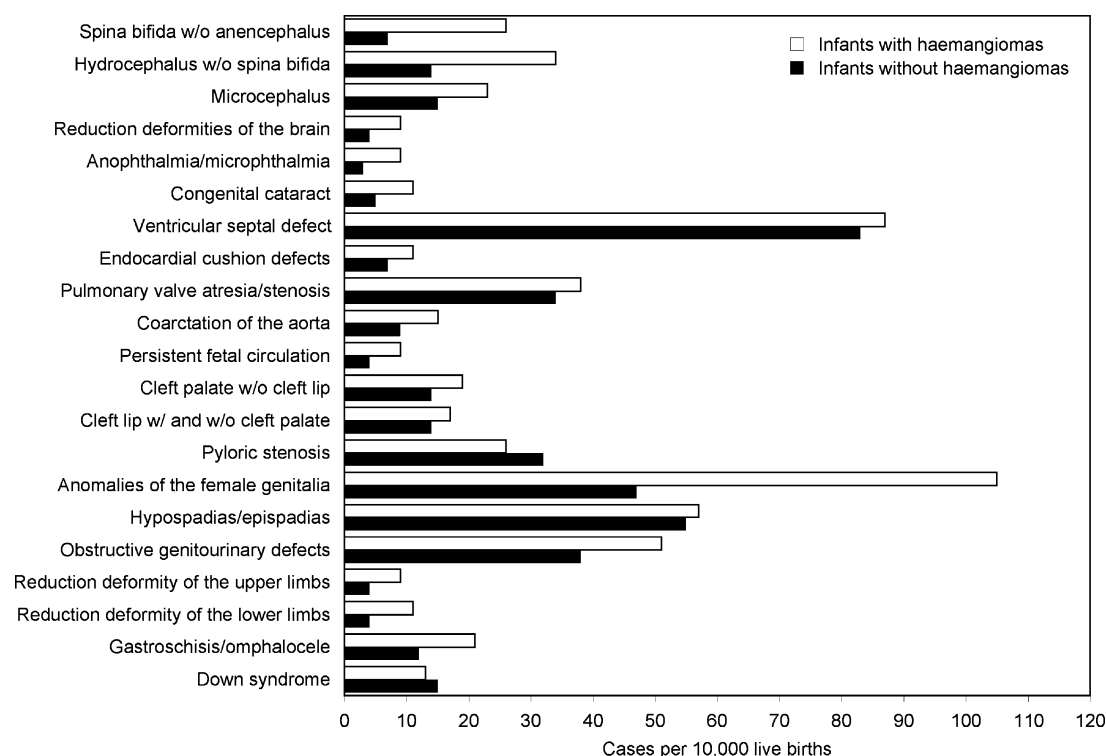


Figure 1. Prevalence of selected congenital malformations among infants with and without haemangioma diagnoses.

mothers, born to married mothers, born to parents in the Air Force, Navy or Marines, and born to parents who were officers in the US military. The military occupation of the sponsoring parent was not associated with haemangioma diagnosis in the final regression model.

The 21 congenital malformation diagnoses chosen for use in cluster analysis, along with their prevalence

among infants with and without haemangiomas, are shown in Fig. 1. Overall, infants with a haemangioma were more likely to have at least one of these congenital malformations (5.2%) than infants without a haemangioma (3.6%). Several of the individual congenital malformations were considerably more prevalent among infants with haemangioma diagnoses than among infants without.

Table 2. Characteristics and odds ratios (OR) for clusters associated with haemangioma diagnosis

Solution	Characterising congenital malformation ^a	Number of infants in cluster	Infants with haemangioma <i>n</i> (%)	OR	<i>P</i> -value
1	<i>Reference cluster^b</i>	452 675	5084 (1.1)		
	Anomalies of the cervix, vagina and external female genitalia	2 228	55 (2.5)	2.23	<0.0001
	Anophthalmia/microphthalmia	141	5 (3.5)	3.24	<0.01
	Hydrocephalus without spina bifida	591	18 (3.0)	2.77	<0.0001
2	<i>Reference cluster</i>	452 751	5097 (1.1)		
	Anomalies of the cervix, vagina and external female genitalia	2 216	55 (2.5)	2.24	<0.0001
3	<i>Reference cluster</i>	454 574	5116 (1.1)		
	Anomalies of the cervix, vagina and external female genitalia	2 229	55 (2.5)	2.22	<0.0001
	Reduction deformities of the brain	158	5 (3.2)	2.90	0.015

^aEach cluster was characterised by a single congenital malformation diagnosis, with all infants in the cluster having that diagnosis.

^bReference clusters comprised the largest clusters in each solution, and consisted primarily of infants with no congenital malformation diagnoses.

Three clustering solutions were identified, as described above, consisting of 12, 12 and 11 clusters (hereafter referred to as solutions 1, 2 and 3 respectively). With the exception of the reference clusters, all clusters were characterised primarily by a single congenital malformation diagnosis, with all infants in a cluster having that diagnosis. Reference clusters comprised the largest clusters in each solution and consisted primarily of infants with no congenital malformation diagnoses. Prevalence of haemangioma within each reference cluster was comparable to the prevalence for the overall sample. Reference clusters and clusters associated with haemangioma diagnosis are described in Table 2.

Haemangioma-associated clusters produced by solution 1 were characterised by: anomalies of the cervix, vagina and external female genitalia (OR = 2.23, $P < 0.0001$); anophthalmia or microphthalmia (OR = 3.24, $P < 0.01$); and hydrocephalus without spina

bifida (OR = 2.77, $P < 0.0001$). Solution 2 produced only one haemangioma-associated cluster which was characterised by anomalies of the cervix, vagina and external female genitalia (OR = 2.24, $P < 0.0001$). Solution 3 produced two haemangioma-associated clusters, characterised by anomalies of the cervix, vagina, and external female genitalia (OR = 2.22, $P < 0.0001$) and reduction deformities of the brain (OR = 2.9, $P = 0.015$).

In logistic regression modelling of congenital malformations related to haemangiomas, three malformations were found to be significantly associated with haemangioma diagnosis (Table 3). Infants with haemangiomas were more likely to be diagnosed with spina bifida without anencephalus (OR = 3.22, [95% CI 1.84, 5.62]), hydrocephalus without spina bifida (OR = 2.03, [95% CI 1.24, 3.34]), and anomalies of the cervix, vagina and external female genitalia (OR = 1.69, [95% CI 1.30, 2.21]).

Table 3. Logistic regression model of relationship between haemangioma and 21 congenital malformation diagnoses in singleton infants born to US military families, 1998–2003

Congenital malformation	All infants (<i>n</i> = 267 495)	Infants with haemangioma (<i>n</i> = 5313)	AOR ^a	[95% CI]
	<i>n</i> (rate per 10 000)	<i>n</i> (rate per 10 000)		
Spina bifida without anencephalus	328 (7.0)	14 (26.4)	3.22	[1.84, 5.62]
Hydrocephalus without spina bifida	642 (13.7)	18 (33.9)	2.03	[1.24, 3.34]
Microcephalus	720 (15.4)	12 (22.6)	1.14	[0.63, 2.07]
Reduction deformities of the brain	198 (4.2)	5 (9.4)	1.16	[0.43, 3.14]
Anophthalmia/micropthalmia	156 (3.3)	5 (9.4)	1.94	[0.73, 5.15]
Congenital cataract	212 (4.5)	6 (11.3)	2.03	[0.87, 4.74]
Ventricular septal defect	3863 (82.7)	46 (86.6)	0.87	[0.63, 1.20]
Endocardial cushion defect	319 (6.8)	6 (11.3)	1.51	[0.61, 3.74]
Pulmonary valve atresia/stenosis	1606 (34.4)	20 (37.6)	0.96	[0.59, 1.56]
Coarctation of aorta	412 (8.8)	8 (15.1)	1.48	[0.72, 3.03]
Persistent fetal circulation	197 (4.2)	5 (9.4)	1.99	[0.82, 4.86]
Cleft palate without cleft lip	660 (14.1)	10 (18.8)	1.14	[0.44, 2.93]
Cleft lip ± cleft palate	640 (13.7)	9 (16.9)	0.92	[0.34, 2.49]
Pyloric stenosis	1467 (31.4)	14 (26.4)	0.90	[0.53, 1.52]
Anomalies of the cervix, vagina, and external female genitalia	2239 (47.9)	56 (105.4)	1.69	[1.30, 2.21]
Hypospadias/epispadias	2568 (55.0)	30 (56.5)	1.24	[0.87, 1.79]
Obstructive genitourinary defects	1769 (37.9)	27 (50.8)	1.26	[0.85, 1.85]
Reduction deformity of the upper limbs	172 (3.7)	5 (9.4)	1.82	[0.75, 4.41]
Reduction deformity of the lower limbs	192 (4.1)	6 (11.3)	2.22	[0.99, 4.96]
Gastroschisis/omphalocele	574 (12.3)	11 (20.7)	1.47	[0.79, 2.70]
Down's syndrome	695 (14.9)	7 (13.2)	0.68	[0.32, 1.47]

^aOdds ratios adjusted for gender, birth status, race/ethnicity, maternal age, maternal marital status, sponsor parent's branch of service, and sponsor parent's rank, and all other congenital malformations in the model.

OR, odds ratio; CI, confidence interval of odds ratio.

Discussion

This study represents the first effort, to our knowledge, to statistically quantify associations between haemangiomas and congenital malformations in a large population-based sample. This research demonstrated that, although congenital malformations occurred in a very small proportion of infants diagnosed with haemangiomas, they were more prevalent among this group than among infants without haemangiomas. Using cluster analysis, a number of groups were identified that were characterised by particular congenital malformations and associated with haemangiomas. Groups characterised by anomalies of the cervix, vagina and external female genitalia were produced by all three clustering solutions, and were significantly associated with haemangiomas. Female infants in these groups were more likely to be diagnosed with haemangiomas than female infants in the reference groups, indicating that these associations were not simply due to the association between female gender and haemangioma diagnosis. Groups significantly associated with haemangiomas, but produced by only one cluster solution, were characterised by anophthalmia or microphthalmia, hydrocephalus without spina bifida, and reduction deformities of the brain.

Multivariable logistic regression, adjusting for selected clinical and parental characteristics, was used to further explore associations between haemangiomas and congenital malformations. The relationship of each congenital malformation with haemangioma diagnosis was assessed, controlling for relationships between all other malformations and haemangioma diagnosis. This approach was intended to emphasise the strongest associations and to compare these with the results of the cluster analysis. Three congenital malformations were identified as being significantly associated with haemangiomas: spina bifida without anencephalus, hydrocephalus without spina bifida, and anomalies of the cervix, vagina and external female genitalia.

Based on the results of both cluster analysis and logistic regression, the most consistently supported congenital malformations associated with haemangiomas were anomalies of the cervix, vagina and external female genitalia, and hydrocephalus without spina bifida. The association between haemangioma diagnosis and spina bifida without anencephalus in logistic modelling was particularly strong, but was not observed in cluster analysis. This may highlight the

value of multiple approaches to exploring associations between rare diagnoses.

Anomalies of the female genitalia, and spinal malformations, including spinal dysraphism, occurring in association with haemangiomas of the lumbar, sacral and perineal regions, have been reported in a number of studies. These malformations are also among those included in the proposed PELVIS (perineal haemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus and skin tag) and SACRAL (spinal dysraphism, anogenital anomalies, cutaneous anomalies, renal and urological anomalies, associated with lumbosacral haemangiomas) syndromes.^{12,14,19,41} Several reports have also described associations between haemangiomas, particularly large facial haemangiomas, and various reduction deformities of the brain,^{16–18,38,42,43} hydrocephalus,^{38,43} and anophthalmia, microphthalmia, or congenital cataracts.^{17,18,38,42,43} All of these malformations are included in the well-established PHACES association (posterior fossa malformations, haemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities, and sternal or ventral defects).¹⁸

Notably, all groups associated with haemangiomas identified by cluster analysis were characterised primarily by a single congenital malformation rather than by constellations of multiple malformations. Other congenital malformations did occur in these groups, but at such low frequencies that no conclusions could be drawn regarding their associations, particularly as the numbers of infants with haemangiomas in these groups were small relative to the group sizes. Specific constellations of congenital malformations associated with haemangiomas may exist, but could not be detected by cluster analysis. Any such constellations are likely to have been so rare that they would not have been apparent among the more prevalent individual congenital malformations. Furthermore, constellations and syndromes that have been described in the literature are not invariant. Rather, they are defined by the presence of haemangiomas with one or more of the malformations included in the constellations. Infants diagnosed with PHACES syndrome, for example, are likely to comprise a very diverse group in terms of the specific malformations of each infant. Cluster analysis attempts to form homogenous groups and it is unlikely that infants with diverse diagnoses would be clustered together in this type of analysis. Also of note was the lack of consistency between the three clustering solu-

tions. This, however, was not unexpected, as *K*-means cluster analysis is highly influenced by the initial seed selection.

Cluster analysis has been successfully applied by at least two different studies to identify groups of cases characterised by different patterns of congenital malformations.^{44,45} However, both studies had some key differences from the current study. Most notably, both analysed much smaller samples of cases ($n = 110$ and $n = 84$), with all cases having at least two birth defects. A similar approach was considered for the current study, but it was decided that such an approach would limit the generalisability of the results. Restricting the sample to just those infants with haemangiomas was also considered. However, doing so would limit the ability to assess patterns of malformations among this group relative to infants without haemangiomas.

The prevalence of haemangiomas in the study population, 1.1%, was low in comparison with other estimates of the prevalence of 4–12% among all infants.^{1–3} This finding is likely to be the result of underdiagnosis of haemangiomas. Infants diagnosed with haemangiomas may represent cases that were more medically or cosmetically concerning. Therefore, observed associations between haemangiomas and congenital malformations could be weaker than the true associations, and other associations may not have been detected. Underdiagnosis of haemangiomas could have occurred differentially among infants with and without congenital malformations. For example, if having a congenital malformation increased the likelihood that an infant with a haemangioma would be clinically diagnosed with the haemangioma, then the observed associations may have been spurious. On the other hand, it is also conceivable that having a congenital malformation might decrease the likelihood that a concomitant haemangioma would be noted if the haemangioma were considered to be insignificant relative to the malformation. In this case, observed associations may have been weakened, while others may not have been detected.

Characteristics of infants diagnosed with haemangiomas in the study population were comparable to what has been previously reported.^{2–4,6–11} Infants diagnosed with haemangiomas were more likely to be female, preterm, white non-Hispanic, and born to older mothers. It has been suggested that a higher prevalence of haemangioma diagnoses in female infants may reflect a greater concern with female cos-

metic issues. Therefore, female infants with haemangiomas may have been more likely to receive medical evaluation than males with haemangiomas.⁴ A related argument can be made for the observed increased prevalence among preterm infants and among infants born to older mothers. Both of these groups are likely to be more closely monitored for any medical problems, by parents as well as by doctors, and therefore may be more likely to have haemangiomas diagnosed. Differences between racial and ethnic groups may have been observed because haemangiomas were more conspicuous on lighter complexions and, therefore, more likely to be diagnosed in white non-Hispanic infants. Differences may also reflect utilisation of health care services. The pathogenesis of haemangiomas remains poorly understood, and biological mechanisms that would explain such associations have yet to be revealed.⁴⁶

These results are subject to a number of limitations, in addition to those previously described. Reliance on ICD-9-CM codes for diagnosis of haemangiomas and congenital malformations can be problematic. Some degree of misdiagnosis or miscoding is likely to exist. Given the number of infants in the data set, validation of all data was not feasible. Validation of small subsets of data is ongoing, but no validation of haemangioma diagnoses has been performed. Also related to the use of ICD-9-CM codes, diagnoses were limited to those for which codes were available.

Another limitation was that some infants may not have remained in the study population for a full year after their birth. Some infants may have died before reaching 1 year of age, while others may have left the military healthcare system if their parent(s) left the military service during their first year of life. This limitation may have been mitigated by the exclusion of infants with unknown information, as demographic information tends to be more complete when records are available for longer periods of time. The lower rate of haemangioma diagnoses among this group is consistent with this reasoning, as haemangiomas often do not develop until some time after birth.

Despite the limitations of this research, a number of potentially important associations were observed in a very large sample of infants. Observed associations were consistent with those observed or proposed in previous reports, but were quantified more specifically in the large population-based sample here. The primary focus of this research was exploratory in nature, and associations between haemangiomas and

congenital malformations identified by these methods are recommended for further study using hypothesis-driven epidemiological methods. Relationships between clinical characteristics and haemangiomas should also be further investigated, with emphasis on minimising the influence of bias.

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