Inheritance Patterns of Infantile Hemangioma

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BACKGROUND AND OBJECTIVE: Infantile hemangioma (IH) includes, among its other risk factors, familial clustering, but a definitive understanding of IH's inheritance model and genetic basis is lacking. Our objective was to collect IH pedigrees in Finland, to study the inheritance patterns of IH within these families, and to analyze the characteristics of familial IHs.

METHODS: We identified 185 patients with IH who visited our vascular anomaly clinic between 2004 and 2007. Based on hospital records and a questionnaire sent to these patients and their families, IH characteristics and family history of IH were studied. We compared characteristics between patients with positive (familial) and negative (sporadic) IH family history. Families with positive IH family history were further interviewed for extended pedigree data.

RESULTS: One-third of our IH cohort’s families reported a family history positive for IH, with IH characteristics and perinatal data between the familial and sporadic cases being similar. IH patients with affected first-degree relatives reported higher long-term discomfort rates than the sporadic cases. Of the 40 families interviewed, 11 included ≥4 IH-affected family members; these were most commonly first-degree relatives (63%). Segregation patterns match with autosomal dominant inheritance with an incomplete penetrance or maternal transmission. We also present a case of monozygotic twins that manifest identical IHs.

CONCLUSIONS: Based on this large number of IH pedigrees, we suggest at least 2 possible mechanisms of inheritance: autosomal dominant and maternal transmission. This study highlights the need for additional genetic studies to define inheritance of this common disease.

WHAT’S KNOWN ON THIS SUBJECT: The cause of infantile hemangioma is multifactorial, with 1 documented risk factor being positive family history. The mode of inheritance and identity of the predisposing genes are unclear.

WHAT THIS STUDY ADDS: This study included a large number of pedigrees with several hemangioma-affected family members. In addition to reported autosomal dominant transmission, we propose that, in some families, hemangiomas may be maternally transmitted. Hemangioma characteristics between familial and sporadic cases are similar.
With an incidence of 4% to 10%, infantile hemangioma (IH) is the most common tumor of infancy. The cause is unknown but considered multifactorial: IH appears more commonly in female subjects, white subjects, twins, and preterm infants, and with advanced maternal age and placental anomalies. Low birth weight is considered the strongest risk factor. The role of genetics in IH is only partially understood.

Most IHs occur sporadically. Familial clustering has been reported, even though genetic predisposition is controversial. Evidence exists that some IHs are inherited. Using information from the Utah Population Database, Grimmer et al reported a twofold increase in the risk ratio for hemangioma among siblings of an affected proband. Walter et al reported 6 pedigrees with an autosomal dominant inheritance of high penetrance; for 3, linkage to chromosome 5q31-33 was proposed. In a small number of patients, genetic variants were associated with germline mutations in the VEGFR2, VEGFR3, and TEM8 genes; these genes regulate major angiogenesis-signaling pathways, suggesting hyperactivation of VEGFR2 signaling in the pathogenesis of IH.

The goal of the present study was to investigate potential familial clustering of IH. We sought to elucidate possible inheritance patterns of IH in families with several affected individuals and to study their geographic distribution in Finland. In addition, we aimed to identify potential differences in IH characteristics and risk factors between familial and sporadic cases.

**METHODS**

**Hospital District**

Helsinki University Hospital, a referral center providing health care services to 1.5 million inhabitants, maintains comprehensive electronic patient records covering all disciplines, excluding primary health care. Its pediatric vascular anomaly clinic serves as the primary referral clinic for all extracranial vascular anomalies. The study protocol was approved by the hospital’s ethics committee.

**Patients**

Patients with IH were identified retrospectively from electronic patient records of the pediatric vascular anomaly clinic based on *International Classification of Diseases, 10th Revision*, diagnosis D18.0 (hemangioma), or Q82.5 (birthmark) from 2004 to 2007, yielding 263 patients; 185 had a true IH. The IH characteristics and risk factors of these 185 children have been studied and published in detail elsewhere. We sent a questionnaire (see Supplemental Figure 4 A and B) to these 185 children with IH concerning perinatal data, current diseases, family history of IH, and current IH-related discomfort (on the basis of a visual analog scale from 1 [no discomfort] to 10 [very significant discomfort]). All families who responded to the questionnaire signed an informed consent form.

Those families who reported a positive IH family history in the questionnaire and allowed re-contact were interviewed in detail by telephone. We specifically asked whether the clinical course of the reported family members’ lesion followed the typical course of an IH and excluded those family members from the pedigrees who had, based on the interview, lesions not fitting to IH. The location and number of IHs were registered, and pedigree information of the affected and nonaffected sides were collected. The birthplaces of the grandparents of the affected index IH-child were recorded to identify possible regional clustering and founder effects. We drew the pedigrees and analyzed the mode of inheritance based on all of these data.

**Statistics**

Patients with ≥1 IH-affected relative were considered as familial cases. We compared the following: (1) all familial IH cases versus sporadic cases; and (2) those familial IH cases with an affected first-degree relative versus sporadic cases. An independent statistician (Datawell Ltd, Espoo, Finland) performed the analyses using NCSS version 8 statistical software (NCSS, LLC, Kaysville, UT). Comparison of continuous variables was performed by using the Mann-Whitney U test, and comparison of categorical variables by using the χ² test; when χ² test preconditions were not met, Fisher’s exact test was used.

**RESULTS**

**Patients**

Of the 185 patients with IH, 136 responded to the questionnaire. Figure 1 summarizes these patients, the number of patients with a positive family history of IH, and the number of families whom we reached for the telephone interview and for the mapping of pedigrees. Based on data from hospital records, ethnic background, sex, and perinatal factors between those responding to the written questionnaire and those not responding were similar. At the time of the questionnaire, the patients were, on average, 10.1 years old (range, 7–20 years).

IH characteristics between familial and sporadic IH cases did not differ regarding perinatal risk factors, IH location, subtype, complications, and interventions. Patients with IH and their first-degree relatives reported a significantly higher mean discomfort rate (2.52 [95% confidence interval [CI]: 1.87–3.16]) compared with sporadic cases (2.03 [95% CI: 1.64–2.42]; *P* = .036). All 3 identical twins of this cohort had first-degree

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relatives with IH, whereas no identical twins appeared in the sporadic IH group (odds ratio: 21.0 [95% CI: 1.05–418.2]; \(P = .046\)). The overall low number of identical twins in the study cohort resulted in a very large CI. Two sets of the monozygotic twins were in concordance for IH, whereas 1 set was in discordance. Of the 11 sets of dizygotic twins with information on IH family history available, 1 set was concordant for IH.

**Familial IH Cases**

Of the 40 families with a positive IH family history who allowed re-contact and who were interviewed by telephone (Fig 1), the closest IH-affected family members were first-degree relatives in 25 (63%), second-degree relatives in 10 (25%), and other more distant relatives in 5 (12%). In addition to the 40 index patients, 81 IH-affected family members were identified. The number of affected family members per pedigree was, on average, 3 (median: 2; range: 2–13). Of the relatives affected with an IH, 27% were men, and 73% were women. We observed no clustering with other inherited diseases or syndromes. No clear correlation was detected regarding IH location or number between the index IH patient and IH-affected relatives. Interestingly, 1 child with a periorbital IH had an identical twin sister who also manifested an IH in the same location (Fig 2).

**Pedigrees**

Of the 40 pedigrees, 22 (55%) were affected on the maternal side, and 12 (30%) were affected on the paternal side. Only siblings of the index IH patients were affected in 6 (15%) of the families. The child’s mother was the most commonly affected relative: for 13 of the 40 index IH patients, the mother had an IH whereas only 4 of the fathers had an IH. Of the 40 families, 11 had ≥4 affected family members. Selected pedigrees are shown in Fig 3. Transmission seemed to follow an autosomal dominant inheritance pattern with incomplete penetrance. Of note, in pedigree 28, the transmission of IH from the father to 3 children may have derived from a strong dominant genetic variant. In 10 pedigrees, maternal transmission with incomplete penetrance was hypothesized (pedigrees 48, 58, 59, 73, 115, 137, 148, 171, 210, and 217). Geographic distribution of places of birth of the affected index patients’ grandparents was wide. No clear clustering or founder effect was detected.

**IH-related Diseases, Syndromes, and Other Inherited Diseases**

Incidence of atopic disease did not differ between familial and sporadic IH cases (15% and 22%, respectively). Several other conditions were present in the cohort in sporadic IH children: 1 child with PHACES (posterior fossa
FIGURE 3
IH pedigrees. The inheritance pattern generally fits autosomal dominant inheritance with incomplete penetrance. In families 58, 59, 115, 148, 210, and 217, the inheritance pattern fits maternal transmission with incomplete penetrance. In families 48 (excluding 48.12 and 48.13), 73 (excluding 73.1), 137 (excluding 137.5) and 171 (excluding 171.1), transmission is possibly maternal when excluding certain affected members.

Symbols
- Male
- IH-affected
- Female
- n = Number of siblings
- Index patient
malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft, and supraumbilical raphe) syndrome, 1 case of Sotos syndrome, 1 case of activated protein C resistance, and 1 case of type 1 neurofibromatosis. One child with a family history positive for IH had Turner syndrome.

**DISCUSSION**

Familial aggregation of IH is infrequently studied, despite its high frequency. We report the largest series of pedigrees with many affected family members. A significant number of patients with IH had a positive family history; more than one-third of the index patients had a positive family history of IH and, in the majority of cases, this finding was in a first-degree affected relative. Due to our study setting, we cannot state the degree to which there is a familial association. IH characteristics of familial and sporadic cases were similar, indicating that familial aggregation does not parallel any specific IH subtype or localization. IH risk factors also did not differ.

Long-term morbidity and discomfort resulting from IHs have previously been linked to head and neck, segmental, and complicated IHs.23,24 In the present study, we evaluated any kind of discomfort due to a residual IH reported by the patients. Surprisingly, the long-term discomfort rate was higher in those IH children with affected first-degree relatives than in the sporadic IH patients. This finding may reflect the burden of having several afflicted members in the same family.

The overall incidence of IH in Finland is unknown. Based on our study setting, we cannot estimate the incidence of familial IH. Because the cause of IH is multifactorial, some affected family members may have developed an IH due to some environmental or other risk factors.19,25 In Finland, which is one of the best-studied genetic isolates, regional clustering in many inherited diseases is still evident, and tracing the birthplaces of patients’ grandparents has revealed a founder effect for several diseases.26-28 In this study, tracing grandparents’ birthplaces revealed no apparent regional clustering.

One factor predisposing a child to IH is multiple-gestation pregnancy.10,29 Studies comparing IH in monozygotic and dizygotic twins found no evidence of zygosity as a risk factor.12,14 We detected 2 discordant monozygotic sets of twins and 1 discordant monozygotic twin but only 1 concordant dizygotic set of twins. The low number of twins in our study prevents drawing further conclusions. To our knowledge, however, no case of concordant monozygotic twins with identically located IHs, as shown in Fig 2, has ever been reported.

The inheritance pattern of IH in the present study mainly followed an autosomal dominant transmission with incomplete penetrance; this outcome therefore supports earlier findings on IH’s inheritance pattern.15-17 Further genetic studies should reveal whether these families also exhibit linkage to chromosome 5q or to other chromosomal loci, or whether they have a predisposition to somatic mutations, as reported in some previous studies.15-22

In addition to the autosomal dominant inheritance, we observed families in which transmission may have been maternal. This finding raises the question of whether the genetic cause in these cases could be linked to mitochondrial mutations. Very few reports involve the role of mitochondria in IH pathogenesis; these concentrate on the intrinsic, mitochondrial apoptotic pathway, which is important for the involution of IH and for any therapeutic mechanism.30 Answering these questions requires further genetic studies to determine whether genetic alterations behind IH’s familial aggregation fit autosomal-dominant or, as shown here, maternal transmission, and what is the identity of these genes.

Our patient cohort was limited to the patients in our IH referral center; this approach excludes innocuous IH cases followed up only in primary health care. The study was also limited by the lack of control group, and we therefore cannot estimate the overall degree of familial clustering of IH. However, sending a questionnaire to a randomly selected control group inquiring into their family history of IH would have yielded many false IH cases, as the term hemangioma is so widely misused.4,31,32 Due to the phenotype variation and nature of IH, it was beyond our scope to determine the exact prevalence of familial IH. The reporting of family history of IH and mapping of the pedigree structures were based on parents’ recall, limiting the study. Due to the natural course of IH, some IH-affected family members may have gone unreported. Conversely, the term hemangioma being used for conditions other than IH may have produced misreporting. The reported IH-affected family members and the pedigrees were confirmed first by written questionnaire and thereafter by telephone interview (the latter of which was used to confirm the typical clinical course of IH in family members). The reporting of perinatal data was partially based on the memory of mothers of children with IH; however, virtually all pregnancies are systematically followed up in maternity clinics in Finland, and all mothers possess a maternity card listing their gestational and perinatal information.

**CONCLUSIONS**

We report the largest series of familial IH in the current literature: 40 IH families, 11 of whom have
First-degree relatives were most commonly affected, and we report for the first time a set of monozygotic twins with identical IH lesions. Familial and sporadic IH cases did not differ in terms of IH characteristics and risk factors. In addition to an autosomal dominant inheritance pattern, we propose that, in some families, IH could be maternally transmitted, thus encouraging further genetic studies.

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ABBREVIATIONS

CI: confidence interval
IH: infantile hemangioma

REFERENCES


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