On infantile hemangiomas
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Risk factors of Infantile Hemangiomas

A case-control study in the Dutch population

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Abstract

Infantile hemangiomas (IH) are considered the most common tumors of infancy, however, despite their frequent occurrence; the exact etiologic determinants for their development remain unknown. Knowing these factors may provide insight on their pathogenesis. Our objective was to detect etiological factors associated with the development of IHs. We performed a cross-sectional screening for IHs in newborns (0-16 months of age) in the general Dutch population. IH-specific and pregnancy-related data were collected in children with an IH. These data were compared in a case-control design using multivariable logistic regression analysis. In a total sample of 2204 newborns, 219 (9.9%) had an IH. The male to female ratio was 1:2. The majority of IHs were located on the trunk (37%). The general practitioner or medical specialist was consulted in a minority of cases (<7%). Amniocentesis [OR 3.6, CI: 1.11, 11.42], breech presentation [OR 2.3, CI: 1.14, 4.44], having siblings [OR 1.55 CI: 1.03, 2.33] and a mean weight at birth <2500 grams [OR 5.0 CI: 1.63, 15.05] were independent factors associated with the development of an IH. Duration of the pregnancy did not differ between both study groups. Our study showed that the prevalence of IHs in the general (Dutch) population is 9.9%. Four etiological factors appear relevant in the development of IHs. These factors may provide clues to its pathogenesis. Additionally, results of therapeutic interventions can more objectively be evaluated.
Introduction

IHs are the most common tumors of infancy.\textsuperscript{1-3} They are recognizable by their typical natural history. Reports on the prevalence of IHs date back to the nineteen fifties and the sixties.\textsuperscript{1,2,4} The nomenclature used to describe IHs changed considerably with the introduction of a new classification system in 1982.\textsuperscript{5} This has obscured the interpretation of the frequencies of these disorders reported thus far.

Although IHs may develop in any body part,\textsuperscript{4} they are preferentially located in the head and neck area.\textsuperscript{5,7} A prevalence of IHs of 22.9\% was described in children with a birth weight lower than 1000 grams.\textsuperscript{8} IH are routinely seen in Caucasians but are relatively uncommon in African or Asian children.\textsuperscript{3,6,9,10} Girls are more likely to be affected than boys in ratios varying from 1-3 : 1.\textsuperscript{1,11}

Suggestions of a higher prevalence of IHs following chorionic villus sampling or amniocentesis exits.\textsuperscript{12-15} Both interventions can cause potential damage to the placenta. Remarkably, a higher ratio of placental pathologic findings was found in mothers of children with this.\textsuperscript{19,20} It may be argued that damage to the placenta, from internal or external origin, could be a possible cause for the development of an IH (the ‘placenta theory’).\textsuperscript{16,21,22} Supporting this theory the endothelial immunoreactivity of IHs and placental villi is similar. They are both positive for the Glut-1 marker; highly selective marker for IHs.\textsuperscript{16-18}

Although they can develop during the first year of life, until now data on the prevalence of IHs were based on hospital records just after birth rather than on data of the general population and confounded by changing definitions. These studies did not use the biologic classification therefore lesions other than IHs may have been included.

We undertook this study to detect which etiological factors in the general Dutch population are predictive for the development of IHs. These factors may provide clues to their pathogenesis. As a consequence, results of therapeutic interventions can more objectively be evaluated.

Patients and Methods

In the Netherlands, a system of infant welfare centres exists where approximately 95\% of all newborn children are routinely examined by a physician at the age of one, three, five, nine, eleven and fifteen months. All newborns, presented at 12 infant welfare centres representative for the general Dutch population between March and June 2002, were included in the study with a follow up of two years.

Before the start of our study, all 13 medical doctors of the cooperating infant welfare centres were instructed about IHs in general, and the goals and methods of the study. The Mulliken classification of cutaneous vascular anomalies was used\textsuperscript{6} to define the presence of an IH. When there was a doubt about the diagnosis, the senior author
(CvdH) was consulted. Before screening informed consent to anonymously collect and record their data for this study was obtained from the children’s parents.

Characteristics of the child (gender, age and birthweight) were filled out for all children visiting the infant welfare centres after start of the screening. After inclusion, the characteristics of the IH, if present, were obtained (size, location on the body, (sub)cutaneous location, number, presence at birth as a so-called precursor lesion, and family history of vascular malformations).

An extensive record was completed by a non-research related nurse by an interview in person at the welfare centre, who was not aware of the presence or absence of an IH in these children. This record contained questions concerning age of the parents, ethnicity, (family) diseases (diabetes, epilepsy), amniocentesis or chorionic villus sampling in this pregnancy, illness during pregnancy (menorrhagia, elevated blood pressure), smoking and alcohol use of the mother, use of anticoagulants or antibiotics during pregnancy, duration of pregnancy, foetal position, placental problems (such as placental infarction or battledore placenta), form of delivery, incubator treatment, presence of congenital disorders, diseases and (skin) disorders during the first three months of life, and sequence of children in the family.

Data analysis
Children who had an IH were included in a case-control study design to analyze possible etiological determinants for an IH. The description and conduct of this design was checked according to the STROBE-statement guidelines. An equal number of controls were randomly selected from the total children seen in the 12 centres, matching for gender and age. Because IHs may not be identified until several months of life, months, all controls were followed up to this age to detect rule out the development of an IH.

For all continuous factors (weight at birth, parental age and duration of gestation) and categorical factors (ethnicity [caucasian/non-caucasian, family diseases [cardiovasc; yes/no, epilepsy; yes/no, DM; yes/no], diseases [HT; yes/no, DM; yes/no] / smoking [yes/no] / alcohol [yes/no] / use of medication [blood diluters; yes/no, antibiotics; yes/no] and illness during pregnancy [menorrhagia; yes/no, HT; yes/no], forms of delivery [natural/caesarean section], foetal position in the belly [head position/breech position], amniocentesis [yes/no] and chorion villus sampling [yes/no] performed) a univariable analysis was performed using the Mann-Whitney or Chi-square tests, respectively. For the factor low birth weight, according to the WHO statistical information system which classifies low birth weight as less than 2500 g, the factor birth weight was dichotomized into two categories of children weighing below or above 2500 grams.

The univariable analysis was used to determinate explanatory factors for development of an IH. Explanatory factors differing between cases and controls with a p-value below 0.10 in the univariable analysis were included in a multivariable logistic regression analysis for determining possible etiological factors, using the backward stepwise
model. The analysis was conducted to identify independent etiological factors associated with the development of IHs and to estimate the odds ratio (OR), including the 95% confidence interval (95%CI) for each significant factor. This enabled prediction of the overall odds for an individual to develop an IH on the basis of the etiological factors detected. Possible interactions between factors (e.g. birth weight and the use of an incubator) were included in the analysis. A p-value <0.05 was considered significant. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 12.0, SPSS Inc., Chicago, IL, USA).

Results
Prevalence
In three months 2204 children were screened of which 219 were found to have an IH according to the Mulliken criteria (prevalence 9.9%). The female to male ratio was 2:1. About 25% of all IHs were precursor lesions present at birth. Nearly 15% of the IHs was located subcutaneously. The majority was located on the trunk (37%), followed by the head-neck area (33%). Of all the IHs in the head-neck area, 75% was located on the scalp and forehead. Eighteen percent of the children had more than one IH.

Because of the IH, 6 percent of the children visited a general practitioner and seven percent a specialist (Dermatologist or Plastic surgeon). The reasons given for these consultations were multiplicity, subcutaneous localization, presentation in the head-neck area or presence at birth of the IHs.

Etiologic factors
The medical records of seven cases in one infant welfare centre were incomplete and had to be excluded. This resulted in 212 cases and 212 randomly selected controls. None of the controls developed an IH until the age of 12 months.

Univariable analysis showed there were significantly more invasive diagnostic procedures like amniocentesis performed in cases presenting with IH (Table 1). Significantly more breech presentations during pregnancy were seen [OR: 2.39; 95%CI: 1.2, 4.7]. Children with an IH were more often the first-born in the family. They were treated in an incubator during the first month twice as often as the controls [OR: 2.19; 95%CI: 1.1, 4.2]. Indications for this treatment were low birthweight, preterm or dysmaturity and low Apgar score. No differences regarding illnesses in the family (epilepsy, diabetes), parental age and congenital abnormalities were seen. Alcohol use and smoking during pregnancy were equal in both groups as for diseases and disorders of the children in the first three months of life. Mean duration of pregnancy was the same for both groups, as were the illness during pregnancy (menorrhagia, elevated blood pressure). Caesarean sections appeared more frequently in the case-group but did not differ significantly from the controls [OR: 1.42; 95%CI: 0.8, 2.42].
**Chapter 4**

**Table 1** Risk factors for developing an infantile hemangioma; a case-control study.

For continuous factors (birth weight, duration of pregnancy) and categorical factors (ethnicity, smoking and illness during pregnancy, caesarean section, breech presentation, amniocentesis) a univariable analysis was performed using the Mann-Whitney or Chi-square tests, respectively.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Children with an infantile hemangioma (Cases;N=212)</th>
<th>Children without an infantile hemangioma (Controls;N=212)</th>
<th>Odds Ratio / WMD*</th>
<th>95% C.I. for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (25th -75th %)</td>
<td>280 days (268-287)</td>
<td>280 days (273-285)</td>
<td>1.9 days</td>
<td>-4.6 , 0.8</td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Sd)</td>
<td>3258 (640) gram</td>
<td>3387 (565) gram</td>
<td>129 gram</td>
<td>-245.2 , -13.8</td>
</tr>
<tr>
<td><strong>Birth weight ≤ 2500 gram</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (12%)</td>
<td>8 (4%)</td>
<td>3.36</td>
<td>1.5 , 7.6</td>
</tr>
<tr>
<td>No</td>
<td>187 (88%)</td>
<td>204 (96%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Origin Caucasoid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>182 (86%)</td>
<td>170 (80%)</td>
<td>1.53</td>
<td>0.9 , 2.6</td>
</tr>
<tr>
<td>No</td>
<td>30 (14%)</td>
<td>42 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Illness during pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- menorrhagia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (6%)</td>
<td>12 (6%)</td>
<td>1.05</td>
<td>0.5 , 2.4</td>
</tr>
<tr>
<td>No</td>
<td>200 (94%)</td>
<td>191 (90%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- elevated blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (12%)</td>
<td>21 (10%)</td>
<td>1.16</td>
<td>0.6 , 2.1</td>
</tr>
<tr>
<td>No</td>
<td>187 (88%)</td>
<td>183 (86%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caesarean section</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (20%)</td>
<td>30 (14%)</td>
<td>1.42</td>
<td>0.8 , 2.4</td>
</tr>
<tr>
<td>No</td>
<td>170 (80%)</td>
<td>182 (86%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breech presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (16%)</td>
<td>17 (8%)</td>
<td>2.39</td>
<td>1.2 , 4.7</td>
</tr>
<tr>
<td>No</td>
<td>178 (84%)</td>
<td>187 (88%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amniocentesis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (6%)</td>
<td>4 (2%)</td>
<td>3.33</td>
<td>1.1 , 10.4</td>
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<tr>
<td>No</td>
<td>199 (96%)</td>
<td>208 (96%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maternal smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (16%)</td>
<td>34 (16%)</td>
<td>0.98</td>
<td>0.6 , 1.6</td>
</tr>
<tr>
<td>No</td>
<td>178 (84%)</td>
<td>178 (84%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incubator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (14%)</td>
<td>17 (8%)</td>
<td>2.19</td>
<td>1.1 , 4.2</td>
</tr>
<tr>
<td>No</td>
<td>182 (86%)</td>
<td>195 (92%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First borne</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>110 (52%)</td>
<td>85 (40%)</td>
<td>1.55</td>
<td>1.03 , 2.33</td>
</tr>
<tr>
<td>No</td>
<td>102 (48%)</td>
<td>127 (60%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*WMD: Weighted Mean Differences*
Caucasian children showed slightly more IHs than non-Caucasians [OR: 1.53; 95%CI: 0.9, 2.6]. The number of mothers that had experienced placental problems, chorion villus sampling or used antibiotics or anticoagulants during pregnancy was too small to draw valid conclusions.

In the multivariable logistic regression analysis, absolute birth weight and incubator-treatment were found to be non-significant etiological factors (Table 2). Children with a birth weight less than 2500 grams had an OR of 4.95 [95%CI: 1.63, 15.05] to develop an IH. The odds to develop an IH for children whose mother had undergone an amniocentesis during pregnancy was 3.56 [95%CI: 1.11, 11.42]. In addition, birth order in a family was associated with the development of an IH: First born children had an odds ratio of 1.55 [95%CI: 1.03, 2.33] to develop an IH compared to following creed. Hence, the change to develop an IH is elevated when a child:
1. Is the first-born in a family, 
2. Had a breech position during pregnancy, 
3. Amniocentesis was performed during the pregnancy 
4. Weighed less than 2500 grams at birth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-born</td>
<td>1.55</td>
<td>1.03 , 2.33</td>
</tr>
<tr>
<td>Birth weight ≤2500 grs</td>
<td>4.95</td>
<td>1.63 , 15.05</td>
</tr>
<tr>
<td>Breech presentation</td>
<td>2.25</td>
<td>1.14 , 4.44</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>3.56</td>
<td>1.11 , 11.42</td>
</tr>
</tbody>
</table>

* 95% confidence interval

**Discussion**

The present study shows that IHs occur in 9.9% of newborns in the general Dutch population. This prevalence is similar to that previously reported in the past. However it is difficult to compare these studies with ours due to the fact that we now use better definitions to diagnose IHs. In addition the populations studied are different. In our study the majority of IHs were located on the trunk and not in the head and neck area. This might be explained by the fact that our study was based on a general-instead of hospital-based population.

Ethnicity of the child was not associated with IHs. This relation is controversial in literature. Haggstrom et al, who concluded IHs occur more likely in white non-Hispanic infants, explained this by a possible different ethnicity distribution in there
study group compared with the general population. This possible referral bias is in our study non-existent as it is based on the general population. Other possible explanations given in literature for this difference between racial groups were due to the lighter complexions of non-Hispanic infants and therefore IHs were more conspicuous and thus more likely to be diagnosed. Chiller et al comparing Hispanic and non-Hispanic infants with IHs found no statistical differences in sex ratios, gestational age and birth weight, although Hispanic infants had slightly higher gestational age and birth weight than non-Hispanic. Evidence is lacking for confirmation of this difference. There is a controversy in the literature concerning the influence of investigations during pregnancy, such as amniocentesis or chorionic villus sampling, on the chance of developing an IH. This is due to lack of follow up or a retrospective study design. Our findings support these suggestions, as amniocentesis was associated with an OR of 3.56 to develop an IH. Could it be possible that an amniocentesis might damage the chorion or placenta? And if so, is it dependent of the experience of the gynaecologist or perhaps the reason why additional examination during pregnancy was needed in the first place. Maternal age was analyzed in this study but not significant. Another finding that supports the 'placental damage hypothesis' is the increasing odds to develop an IH when the child is the first new-born in a family. First pregnancies are more often associated with pre-eclampsia. Pre-eclampsia is also related with a higher prevalence of IH. Comparison of IHs in preterm and term infants showed a significant higher incidence of multiple gestation, placental anomalies, infertility treatments and maternal pre-eclampsia. Its is unclear whether the pre-eclampsia, placental abnormalities, or low birth weight affects the prevalence of IH. We recognize these as confounding factors as they are usually closely related. As pre-eclampsia was not studied as an etiologic factor in this study, further research in these specific variables could clarify the aetiology of IHs.

Breech presentation during pregnancy was associated with increased prevalence of IH. Breech presentation is in general more likely to be associated with a caesarean section. Which of these is a cause for development of IHs or an additional consequence remains unclear.

We found that children with birth weight lower than 2500 grams had an increased risk to develop an IH, which was also suggested in previous research. According to Amir children with a low birth weight (up to 1000 grams) are at a higher risk to develop an IH. In our study only one child weighed less than 1000 grams, so this statement could not be verified. Once more it should be noted that birth weight is reversely related to pathologic placental findings. It remains unclear if there is a direct association between low birth weight and IHs or perhaps the causes or consequences of low birth weight. Further research on these specific factors is necessary.

Incubator-treatment appeared to be a significant factor for the development of an IH in the univariate analysis. The indication for this treatment is inextricably related to prematurity, difficult start / low Apgar scores, or low birth weights. Though we knew
which children had an incubator treatment we did not know the exact reason why. No correlation was found between incubator treatment and pregnancy duration or a birth weight less than 2500 grams. If there was a correlation, the significance of incubator treatment could be attributed to these factors. The fact that there is no correlation found could be due to lack of data what the reason for incubator treatment was or additional unknown factors triggering the onset of the IH. One previous study indicated that preterm children have a higher chance of developing an IH.\textsuperscript{8} In this study the definitions of preterm were based on weight rather than duration of pregnancy.

Propranolol, a non-selective β-blocker was serendipitously discovered by a France group in 2008 for treatment of an IH.\textsuperscript{33} Reports on the mechanism, by which propranolol causes this dramatic effect, show an important role for the renine-antiotensine system.\textsuperscript{34} β-blockers reduce the renine activity and thereby decreasing Angiotensine II and vascular endothelial growth factor (VEGF) favouring involution, rather than proliferation. High levels of rennin are found in Caucasians compared with blacks\textsuperscript{35}, females compared with males\textsuperscript{36}, premature compared with full-term infants\textsuperscript{37} and infants compared with adults.\textsuperscript{38} This support our clinical observation of an increased change to develop an IH if an infant weighed less than 2500 grams at birth and the male : female ratio. It could also explain the spontaneous regression of IHs; as children grow older the renine levels decrease. Further research on the insight of this mechanism could provide us more clues for the etiology of IHs.

Due to the general-based population, in our study, the numbers of premature and low birth weight children are small. The consequence of this limitation is that further research is required to explore the relationship between IHs, preeclampsia, placental abnormalities and the use of an incubator.

In conclusion, our study showed that the prevalence of IHs in the general (Dutch) population is 9.9%. Four etiological factors appear relevant in the development of IHs: amniocentesis, birth weight below 2500 grams, breech presentation, and being the first-born in the family.
Chapter 4

Reference List


Garzon MC, Drolet BA, Baselga E, Chamlin SL, Haggstom AN, Horii K et al. Comparison of Infantile Hemangiomas in Preterm and Term Infants: A Prospective Study. Archives of Dermatology 2008; 144(9): 1231-1232


