On infantile hemangiomas
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Prevalence of infantile hemangiomas among children with Down syndrome

Running title: Infantile hemangiomas and Down syndrome

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Chapter 3

Abstract

Aim Our aim was to establish the prevalence of infantile hemangioma in a cohort of children with Down syndrome

Methods In a national cohort of 196 children born with Down syndrome in The Netherlands, from June, 1999, to August, 2001, a retrospective study for the presence of infantile hemangiomas was performed by checking their medical records and sending out a questionnaire to the parents.

Results Of the 196 medical records studied and 104 returned questionnaires, none of these provided any reference to a skin eruption resembling infantile hemangioma or any other vascular anomaly.

Conclusion We observed a zero prevalence of infantile hemangioma in a cohort of 196 children with Down syndrome that may support the hypothesis that an over-expression of chromosome 21 related anti-angiogenic factors (ADAMTS1, DSCR1 DYRK1a, Collagen XVIIIa /endostatine) protects these children against infantile hemangioma.
Introduction

Infantile hemangiomas are benign vascular solid tumors that typically appear within the first weeks after birth. They have a common characteristic presentation of rapid growth and slow, spontaneous involution but they vary in size, number, anatomical localization, depth of the lesion (superficial, deep or mixed), and morphological subtype (localized or segmental). This gives them a wide variation in appearance: from a little single bright red tumor or a plaque like swelling covering half the face, to a rounded swelling protruding under a bluish skin. Infantile hemangiomas occur in 5-10% of newborns with a male-to-female ratio of approximately 1:2.5.1–6 Caucasian infants are affected two times more often than non-Caucasians.4 Furthermore, infantile hemangiomas tend to occur two to three times more often after chorionic villus sampling, a procedure that may lead to maternofetal transfusion and placental embolization7,8, a procedure more often performed in cases where the maternal age is over 35 years.9,10 Although the exact mechanisms underlying the occurrence and involution of infantile hemangiomas are incompletely understood, an increased expression of angiogenic growth factors11,12 and seeding13 or embolization14,15 of placental endothelial cells have been suggested to cause this vascular solid tumor.

Malignant solid tumors occur less often in children with Down syndrome (trisomy 21) as compared to the general population.16–20 This raises the question whether, or not, the prevalence of infantile hemangiomas among children with Down syndrome is also lower. To date, only Greene et al.21 and Bukowinski et al.22 reported that hemangioma-like anomalies are rare among children with Down syndrome but both these studies lacked any verification of the true nature of the studied anomaly. Hence, the aim of the current study was to establish the prevalence of infantile hemangioma in a cohort of children with Down syndrome as confirmation of a lower prevalence may shed light on the etiological mechanism of this benign vascular tumor.

Materials and Methods

A national cohort of 196 children with Down syndrome born in The Netherlands between May, 1999 and July, 2001,23 was retrospectively studied for the presence of infantile hemangiomas. All children had had study visits at the ages of 3,5 weeks and 2, 6, 12, 18 and 24 months consisting of an interview with the parents and a detailed physical examination for any deformity of the child, including inspection of the skin. In 2010, all 196 medical records were checked for any reference to a vascular anomaly or any other skin eruption that might resemble such an anomaly. Furthermore, questionnaires containing a description of the appearance and natural behaviour including two photographs of classical examples of infantile hemangiomas (Figures 1 and 2, See Appendices, page 134) were sent to the parents of the 196 children. We
asked the parents if their child had had a infantile hemangioma any time during infancy. To increase the likelihood that we would not miss any infantile hemangiomas, we also asked the parents if their child ever had a skin deformity resembling the description and third, they were asked if any skin problems had occurred of which they were not sure whether, or not, they resembled the previous description. The parents were explicitly asked to respond positively to any of the questions when in doubt. Six weeks after this first mailing, a reminder letter was sent to non-responders to increase participation. When the medical record or the parents reported any skin deformity, parents were contacted to verify the true nature of the deformity. In these cases, the parents were asked to provide an extensive description of the skin deformity and photographs of the child that showed the skin deformity. In addition, the medical record held by the general practitioner was checked for information on the skin deformity. The two principal investigators (MJH and CMAMH) judged the description, photographs and medical records in joint consensus.

Statistical analyses were done with SPSS for windows, release 16.0 (Chicago, IL USA). The Fisher’s Exact Test was used for determining expected and measured prevalence of infantile hemangiomas. A \( p \)-value of 0.05 was accepted as indicative of statistical significance.

Results

Of the 196 medical records studied, none provided any reference to a skin eruption resembling infantile hemangioma or any other vascular anomaly. Since their inclusion in the original cohort study, three of the 196 children had died of non-hemangioma-related causes. Thirteen others were lost to follow-up. A total of 104 of the remaining 180 sent out questionnaires (57.8%) was returned. Mean current age of the 103 caucasian and 1 non-caucasian children was 7.3 years (SD, 0.79). None of the responders reported the occurrence of an infantile hemangioma in their child. Three parents expressed doubts concerning a skin deformity of their child but they were diagnosed as a salmon patch in one child and eczematous skin disorder in the other two.

Discussion

We present the first study reporting the true prevalence of infantile hemangioma in a national cohort of children with Down syndrome. We found no reference to the disorder in any of the medical records of the 105 boys and 91 girls with trisomy 21 that were originally included in the cohort and were submitted to frequent physical examinations during the first 2 years of life. This holds true even though we would have expected 19 children with an infantile hemangioma to occur among newborns without trisomy 21
Prevalence of infantile hemangiomas among children with Down syndrome

Furthermore, we proved no infantile hemangioma to have occurred in the 55 male and 49 female children with Down syndrome on whom we received additional information by questionnaire while we would have expected 10 in normal controls ($p < 0.000$). This holds true, even though the mean maternal age of these children and the number of chorionic villus samplings, both predisposing for the occurrence of infantile hemangiomas, is expected to be higher in our Down syndrome cohort than among children without trisomy 21.24,25 Our observations give rise to the question whether, or not, there is a specific inhibitor signal that prevents children with Down syndrome from developing infantile hemangiomas.

Potential methodological limitations
Before we discuss the possible answer to this question, some potential limitations of our methodology need to be addressed. As such, the relatively low response rate of the questionnaire (57.8%) may have resulted in an underestimation of the true prevalence of infantile hemangioma. However, all 196 hospital records, containing the detailed reports of repeated physical examinations directed at phenotypic abnormalities, were checked as back-up and these, equally, did not contain any reference to a vascular anomaly. Second, the time passed since birth and the possible occurrence and involution of an infantile hemangioma among our study cohort was approximately 7 years and this may have resulted in an underreporting of the disorder by the parents. Still, parents were explicitly asked to respond positively to any of the questions in case of doubt, thus triggering the additional steps of our research. Third, in the Van Trotsenburg study23 ten children were excluded because of a gestational age below 36 weeks. Prematurity is associated with a higher incidence of infantile hemangiomas.4 However, even if we would assume that all ten had a infantile hemangioma, we still have only half of the expected number of children with a infantile hemangioma ($p=0.014$). Fourth, in the Van Trotsenburg study, children with pre-existent hypothyroidism were excluded. In the literature several cases of PHACES syndrome with associated congenital hypothyroidism have been reported. Although the number of cases is low, there might be an association between PHACES and congenital hypothyroidism. However, no cases have been reported with a combination of Down and PHACES syndrome, making underreporting of infantile hemangiomas as part of PHACES syndrome in a Down cohort unlikely. Furthermore hypothyroidism can be caused by type 3 iodothyronine deiodinase in infantile hemangiomas26; however, up to this date this has only been reported for hepatic hemangiomas, not for hemangiomas of the skin.

Possible implications of our observations
To date, several studies demonstrated that Down syndrome is associated with a unique tumor-profile with an increased incidence of some malignancies while others are rare.17,18 As such, malignant solid tumors like neuroblastoma, lymphoma, soft tissue
sarcoma and Wilm’s tumors occur less often in individuals with Down syndrome.\textsuperscript{16,17,19,20} The expansion of such tumors is associated with pathologic angiogenesis regulated by a balance of pro-angiogenic and anti-angiogenic factors produced both by tumor cells, and surrounding stromal cells.\textsuperscript{27,28}

Infantile hemangioma is the result of increased angiogenesis, the degree of which is depending on the disruption of balance between angiogenic and anti-angiogenic factors.\textsuperscript{29–34} Proliferating infantile hemangiomas are marked by a significantly increased serum level of vascular endothelial growth factor (VEGF)\textsuperscript{35} as a result of up-regulated genes establishing components of the VEGF system, such as angiopoietin and Notch 4.\textsuperscript{36} The fact that infantile hemangiomas appear in neonates that have very short been subjected to environmental influences, suggests that genetic factors play an important role in their development.\textsuperscript{37,38} The extreme low prevalence of infantile hemangiomas, like malignant solid tumors and angiogenesis-related diseases such as diabetic retinopathy\textsuperscript{39} and atherosclerosis\textsuperscript{40} among the Down syndrome population more specifically suggests a possible protective effect from the additional copy of chromosome 21.

Several genes with anti-angiogenic activity have been identified on chromosome 21 (Table 1)\textsuperscript{34,41–48} The increased expression of DSCR1 in a mouse model of Down’s syndrome showed significant suppression of tumor growth.

\textbf{Table 1} Anti-angiogenic factors regulated by genes on chromosome 21 with their function and pathway.

<table>
<thead>
<tr>
<th>Anti-angiogenic factor</th>
<th>Gene</th>
<th>Pathway</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam TS-1</td>
<td>21q21.2</td>
<td>Blocks VEGF receptor2 phosphorylation</td>
<td>Suppression of endothelial cells, migration and proliferation</td>
<td>44</td>
</tr>
<tr>
<td>DSCR1</td>
<td>21q22.12</td>
<td>Suppression of the calcineurin NFAT pathway</td>
<td>Decrease VEGF expression</td>
<td>41, 45, 47</td>
</tr>
<tr>
<td>DYRK1a</td>
<td>21q22.13</td>
<td>Suppression of the calcineurin NFAT pathway</td>
<td>Decrease VEGF expression</td>
<td>40</td>
</tr>
<tr>
<td>Collagen XVIIIa /endostatine</td>
<td>21q22.3</td>
<td>Receptors on endothelial cells - influx of extracellular calcium - down regulation of genes expression during endothelial growth - decrease migratory capacity</td>
<td>Suppression in expression of VEGF</td>
<td>42, 43, 46</td>
</tr>
</tbody>
</table>
DSCR1, together with DYRK1a, suppresses the calcineurin signalling pathway that may lead to a deficit in tumor angiogenesis by blocking VEGF activation of endothelial cells. VEGF is responsible for a dose-dependent effect during vasculogenesis, allowing endothelial cells to proliferate, migrate, and assemble in tubes. Of the chromosome 21 related anti-angiogenic factors, endostatin, a cleavage product of collagen XVIII encoded by the COL18A1 gene, shows increased levels among individuals with Down syndrome. Evidence suggests that endostatin suppresses the expression of VEGF, because the antitumor effect of endostatin involves downregulation of VEGF in tumor cells. The fourth candidate to play a protective role against hemangioma in DS patients is ADAMTS1, a metalloprotease which blocks VEGFR2 phosphorylation by binding and secretion of VEGF-165 leading to suppression of endothelial cell proliferation.

Our observations support the hypothesis that systematic up-regulation of this and other chromosome 21 related anti-angiogenic regulators prevent the development of infantile hemangioma in children with Down syndrome. If this proves to be true, this could help identify a drugable target to suppress growth of benign and malignant solid tumors.

**Conclusion**

We observed a zero prevalence of infantile hemangioma in a cohort of 196 children with Down syndrome and postulate that this observation supports the hypothesis that an over-expression of chromosome 21 related anti-angiogenic factors protects these children against infantile hemangioma.
Chapter 3

Reference List

Prevalence of infantile hemangiomas among children with Down syndrome

Chapter 3