On infantile hemangiomas
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Introduction on infantile hemangiomas
and outline of the thesis
Introduction

Infantile hemangiomas are benign vascular tumors. The clinical features of infantile hemangiomas are typical: while in 25% of cases a so called precursor lesion such as local teleangiectasias or blanching can be seen at birth, a vascular tumor appears in the first weeks or months after birth. An initial period of rapid growth, the proliferation phase, is followed by a slow regression of the tumor; the involution phase. Distinctive for the proliferation phase is the endothelial growth and hypercellularity. This proliferation phase starts during the first months after birth and reaches its peak size at the age of 3 to 12 months. The typical infantile hemangioma undergoes a slow and steady involution that starts at an average age of 12 months and continues for three to seven years. In the involution phase, the cellularity and size will decrease and the color will fade to a grey hue, usually starting in the center of the tumor. Its firmness will also decline. As a rule of thumb, 50% of infantile hemangioma show complete involution by age 5 years and 70% by age 7 years. The remainder may take an additional three to seven years to complete the process of involution. But even after complete involution, permanent sequelae like cutaneous residua varying from scar formation, telangiectasia, redundant skin and atrophy, to fibrofatty tissue, may be present in up to 50 % of the affected children.

Infantile hemangiomas may be subdivided in accordance to the depth of soft tissue involvement: superficial, deep, and mixed. Additionally, they may be divided by whether they are spatially confined (localized), or cover a territory (segmental). Differences in growth of these subtypes show that segmental and deep infantile hemangioma tend to grow later and longer then localized and superficial infantile hemangioma. Segmental infantile hemangiomas are more often associated with the so-called PHACES and LUMBAR syndromes. PHACES is an acronym that stands for posterior fossa anomalies in the brain, (large facial infantile) hemangioma, arterial and cardiac abnormalities, eye abnormalities, and sternal clefts. The LUMBAR syndrome is a combination of lower body infantile hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies. Similar to the LUMBAR syndrome but differently named is the PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) syndrome.

Historical background

The term ‘haemangioma fructuosum’ is the Latin name of infantile hemangioma. In the ancient days, people used to think that infantile hemangiomas originated from the longing for strawberries of the mother during pregnancy. In the eighteenth century Turner (1714) wrote in his work *De Morbis Curaneis: A treatise of Disease Incident*
Introduction on infantile hemangiomas and outline of the thesis

to the Skin a detailed mechanism for these birth marks; ‘we shall take notice of some monstrous Births, or otherways deform’d and blemisch’d by Marks from the strong Imagination of disappointed Longings of the Mother’.\textsuperscript{21} Hence, infantile hemangiomas were given multiple names such as strawberry-, capillary-, juvenile- or cellular hemangioma, angioma simplex, or angioma cavernosum. On the other hand, the term ‘hemangioma’ was used as a generic word to describe a variety of vascular lesions with different etiology and natural histories.

Clarity came in this pool of confusing terminology only when Mulliken and Glowacki proposed a biological classification system for vascular anomalies, in 1982.\textsuperscript{1} A formal classification based on clinical course and histology of the anomaly was set forth in 1996 by the International Society for the Study of Vascular Anomalies.\textsuperscript{17–19} This system is currently the most accepted framework to classify vascular anomalies. Further research results in expansion and further completion of this framework and the understanding of vascular anomalies.

According to this classification, vascular anomalies are differentiated into vascular tumors or vascular malformations (Table 1). This distinction states that vascular tumors are neoplasms of the vasculature and include infantile hemangioma, Rapid Involuting Congenital Hemangioma (RICH), Non Involuting Congenital Hemangioma (NICH), tufted angioma, kaposiform hemangiomendothelioma, puogenic granuloma, and hemangiopericytoma. Vascular malformations are structural deficits of the vasculature and can be subdivided into simple and (well-defined) combined vascular malformations.
Table 1 Classification of Vascular Anomalies

<table>
<thead>
<tr>
<th>VASCULAR ANOMALIES</th>
<th>VASCULAR TUMORS</th>
<th>VASCULAR MALFORMATIONS</th>
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<tbody>
<tr>
<td>INFANTILE HEMANGIOMA</td>
<td>- Infantile Hemangioma</td>
<td>SIMPLE</td>
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<tr>
<td>INFANTILE HEMANGIOMA</td>
<td>- Rapid Involuting Congenital Hemangioma</td>
<td>- Capillary</td>
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<tr>
<td>INFANTILE HEMANGIOMA</td>
<td>- Non Involuting Congenital Hemangioma</td>
<td>- Venous</td>
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<td>INFANTILE HEMANGIOMA</td>
<td>- Tufted angioma</td>
<td>- Lymphatic</td>
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<tr>
<td>INFANTILE HEMANGIOMA</td>
<td>- Kaposiform hemangiomendothelioma</td>
<td>- Arterial</td>
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<td>INFANTILE HEMANGIOMA</td>
<td>- Pyogenic granuloma</td>
<td>- Arteriovenous</td>
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<tr>
<td>INFANTILE HEMANGIOMA</td>
<td>- Hemangiopericytoma</td>
<td>COMBINED</td>
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Diagnosis of infantile hemangioma

In 93% of all cases, the diagnosis of infantile hemangioma is a clinical one based on anamnesis and physical examination. In cases where the clinical course is not typical of infantile hemangioma, additional investigations like sonography and MRI can offer a solution. A biopsy should be performed whenever doubt remains. Immunological staining with Glucose Transporter 1 (Glut-1) can then differentiate infantile hemangioma from vascular malformations.

Treatment of infantile hemangioma

Because 80 to 90 per cent of all infantile hemangiomas resolve without sequelae, these do not need treatment. Still, a ‘wait and watch policy’ does not infer that nothing should be done. Insecurity arises together with the proliferating infantile hemangioma. Most parents wonder whether their child will psychologically suffer from this tumor. These parents must be given a thorough explanation of the natural history of the particular hemangioma. It may be helpful to expand such an explanation with example pictures. Frequent visits for re-evaluation during the proliferation phase and evaluation by use of repeated photography of the tumor are also helpful.

A minority of 10% of all infantile hemangiomas causes problems resulting from painful ulcerations, bleeding, or location specific risks such as obstruction of the airway or visual axis and involvement of liver. Early active treatment is obligatory in these specific cases. Treatment options consisted of topical antibiotic or hydrocolloid dressings if ulcerations occurred and dye laser treatment to reduce the possible pain resulting from
the ulceration.\textsuperscript{29–31} In case of bleeding, compression must be applied but hemostatic suturing may be needed. To reduce complications, corticosteroids (systemically or intralesional), vincristin, laser treatment, or operative resection may be indicated. The large variety of treatment options shows that there is no ultimate treatment strategy.\textsuperscript{2,32,33} The accidental discovery that propranolol, administered for decreased cardiac output in a child with an infantile hemangioma in the proliferation phase, led to permanent regression of the lesion changed this.\textsuperscript{34} This beneficial effect of oral propranolol is confirmed by other reports.\textsuperscript{35,36} An increasing number of reports currently propagate propranolol as first line therapy for infantile hemangioma in both the proliferation, and the involution phase.\textsuperscript{35–38} Beside this new treatment option, topical β-blocker submerged to be a successful therapy of infantile hemangioma.\textsuperscript{39,40} Topical timolol therapy can even offer a solution in cases of ulcerated infantile hemangioma.\textsuperscript{41} Surgical correction may be warranted in case of residual sequelae after the regression of the hemangioma.\textsuperscript{2,33}

**Outline of the thesis**

Data on the prevalence of infantile hemangiomas were based on studies from the sixties in the past century, when confusing terminology hampered the proper registration and comparison of anomalies. Terms as cavernous hemangioma instead of venous malformation polluted prevalence numbers on hemangioma in the literature and thus hampered insight in complications and treatments outcomes. New studies using the definition of Mulliken and Glowacki on infantile hemangiomas and other vascular anomalies are lacking. Hence, the first step in understanding infantile hemangiomas was to clarify the extent of this disorder by determining the population-based prevalence. In **Chapter 2**, we present our research on the prevalence of infantile hemangioma in the Netherlands using the definition proposed by Mulliken et al.\textsuperscript{1} Over the years, we noticed that we newer saw a child with both infantile hemangioma, and Down syndrome (trisomy 21). A literature search revealed a reduced occurrence of malignant solid tumors among children with Down syndrome as compared to the general population. This raises the question whether, or not, the prevalence of infantile hemangiomas among children with Down syndrome is also lower. Could they possibly be protected against benign vascular tumors like infantile hemangiomas by the third chromosome 21? In **Chapter 3**, we describe our study after the prevalence of Down syndrome among our patients and give an overview of possible pathways for (anti) angiogenesis as a step to provide clarity in the developing mechanisms of infantile hemangioma.

Despite their frequent occurrence, the exact etiology of infantile hemangiomas remains unclear. Various theories arose why certain children develop an infantile hemangioma while others do not. Could placental damage be the cause of an infantile hemangioma?
Chapter 1

or are there other unidentified etiologic factors? With a case-control study we attempt to identify etiologic factors possibly contributing to the origins of infantile hemangioma. **Chapter 4** is devoted to clarify some parent- and patient-related etiologic factors in infantile hemangioma development.

Due to heterogeneity in presentation the diagnosis of infantile hemangioma is not always as simple as it seems when one is confronted with a newborn with a growing tumor. In case of misdiagnosis of a malignancy as an infantile hemangioma the ‘wait and watch’ policy leads to delay or omission of optimal treatment. Therefore, we report on seven children with a malignancy that was initially referred under the diagnosis “infantile hemangioma” in **Chapter 5**.

Periorbital infantile hemangiomas may affect visual development. Close observation and medical treatment are advised for preservation of vision. After the discovery of the beneficial effect of propranolol, it quickly became the first treatment of choice for infantile hemangiomas. Still, comparisons with ‘conventional therapies are lacking in the literature. In **Chapter 6**, we retrospectively compare our treatment outcomes using intralesional corticosteroid injections versus propranolol for periorbital infantile hemangiomas.

Once the correct diagnosis is made, further policies are discussed; *in casu* a ‘wait and watch policy’ with repeated evaluations, or immediate treatment. A period of insecurity begins for most parents. Their children have to deal with the possible burden of a (visible) deformity. According to the parents, children definitely suffer from this. Little is known of the psychological impact that infantile hemangiomas have on children and their parents. In an attempt to map this impact, we conducted a study to investigate the psychological sequelae of infantile hemangiomas on children and their parents described in **Chapter 7**.

We further reviewed and evaluated the total body of currently available and relevant studies on the psychological impact of infantile hemangiomas on children and their parents, in **Chapter 8**.

Finally, in **Chapter 9**, the results from these studies are summarized and our conclusions are put into perspective.
Introduction on infantile hemangiomas and outline of the thesis

Reference List

Chapter 1


