On infantile hemangiomas
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Summary
In **Chapter 1**, a general introduction on infantile hemangiomas including a historical background, and the outline of this thesis are provided.

In the first part of this thesis, we present the research we did to better understand infantile hemangiomas. In **Chapter 2**, we present current data on the prevalence and characteristics of infantile hemangiomas found by use of a cross-sectional study and using the definition of infantile hemangioma proposed by Mulliken. During three months, all children aged 0-16 months who presented for regular check-ups at child health centers in the Tilburg area, the Netherlands, were examined by physicians for the presence of infantile hemangiomas. The characteristics of the children with an infantile hemangioma were recorded and parents were asked for more specific information. Of the 2204 children included, 219 (10%) had 256 infantile hemangiomas. In 24% of children it was already present at birth as a precursor lesion. Of the 256 infantile hemangiomas, 15% were located subcutaneously, 33% were located in the head-neck area and 37% on the thorax. Of the 84 infantile hemangiomas in the head-neck area, 75% were located on the scalp and forehead. Of the 219 children, 7% and 6% visited a general practitioner or specialist regarding the infantile hemangioma, respectively. These physicians were consulted particularly when the infantile hemangioma was present at birth, located subcutaneously, located in the head-neck area, or when multiple infantile hemangiomas were present. With these findings we provide the present prevalence and characteristics of infantile hemangiomas in the general population and provide more insight in the composition of infantile hemangiomas in a hospital-based population.

In **Chapter 3**, we establish the prevalence of infantile hemangioma in a cohort of children with Down syndrome since patients with Down syndrome have a reduced risk of solid tumors. We performed a retrospective study in a national cohort of 196 children born with Down syndrome in the Netherlands for the presence of infantile hemangiomas by checking their medical records and sending out a questionnaire to the parents. Of the 196 medical records studied and 104 returned questionnaires we observed a zero prevalence of infantile hemangioma. This may support the hypothesis that a triple chromosome 21 provides extra anti-angiogenic related factors which protects these children against infantile hemangioma.

**Chapter 4** is devoted to parent- and patient-related etiologic factors in infantile hemangioma development. With a case-control study we set out to identify etiologic factors in order to provide insight on the pathogenesis of infantile hemangiomas. Parents-, patient- and pregnancy-related data were collected in children with a infantile hemangioma. These data were compared in a case-control design using multivariable logistic regression analysis. We found four factors to appear relevant for the development of infantile hemangiomas. Amniocentesis, breech presentation, being
first-born, and a birth weight ≤2500 g were independent factors associated with the development of a infantile hemangioma. Duration of pregnancy did not differ between study groups. These factors may provide clues to its pathogenesis.

Not every appearance of infantile hemangiomas abides by the typical clinical presentation. In Chapter 5, we present the history of seven children that were referred for infantile hemangioma but turned out to have a malignancy. We reviewed all 423 children referred with a diagnosis of infantile hemangioma from April, 2003, through December, 2009. Their records were studied to determine the definitive diagnosis. The characteristics of the seven children with a malignant diagnosis (2%) and of their diagnostic process were retrospectively analyzed. The diagnosis were a rhabdomyosarcoma (n = 2), a sarcoma (n = 1), a poorly differentiated round and spool cell sarcoma (n = 1), a nerve sheath sarcoma (n = 1), a dermatofibrosarcoma protuberans (n = 1), and a lymphoma (n = 1). Early age malignant tumors can mimic benign infantile hemangioma. In cases where the diagnosis of infantile hemangioma is equivocal, biopsy has to be performed in a specialized center to prevent delay or omission of proper treatment.

In Chapter 6 we present our retrospectively comparison of treatment with intralesional corticosteroids injections and oral propranolol in children with a periorbital infantile hemangioma. All children diagnosed with an infantile hemangioma by the multidisciplinary task force of the Academic Medical Center in Amsterdam from July of 2004 through December of 2011 and treated with intralesional corticosteriods (29) or propranolol (14) were included. Intralional corticosteroid injections contained a mixture of Kenacort and Solumedrol. Oral propranolol treatment was given with a maximum of 3 mg/kg/day. In case no further improvement was seen by the multidisciplinary task force for infantile hemangiomas, treatment was stopped. Type of treatment, duration, complications and additional therapies (non invasive and invasive) were tracked. Outcomes of visual measurements, at the beginning of the therapy and at the end, were divided in an amblyopic scale from one (no amblyopia) to five (severe amblyopia). We found the duration of therapy to be significant longer in the intralesional corticosteroid group. No major complications occurred in both groups. No difference was observed in the numbers of additional non-invasive therapies but more invasive therapy was additionally needed in the intralesional corticosteroid group. The levels of amblyopia at the start and end of therapy did not differ significantly and the median absolute improvement did not significantly differ between both groups. We conclude that a more rapid response to the propranolol therapy leads to a more aggressive prevention of vision damage and additional therapy.

To date, little was known of the psychological impact that infantile hemangiomas have on children and their parents. In the second part of this thesis, we assess the health-
related quality of life (HRQoL) of children aged 1-15 years with an infantile hemangioma and their parents in comparison with healthy children, and the impact this has on their life.

In Chapter 7 we report a study to investigate the psychological sequelae of infantile hemangiomas on children and their parents described by sending age-specific validated HRQoL and infantile hemangioma-specific questionnaires to all children seen at the Academic Medical Center in Amsterdam at the plastic surgery or dermatology departments. With an 85% response rate (201 children and their parents), the majority of parents and patients with an infantile hemangioma are not negatively affected by it. In the specific infantile hemangioma questionnaire, high scores on feelings of disbelief and panic during the growing phase are given by parents and patients agree with the statement on whether their life would be different without an infantile hemangioma, especially when the infantile hemangioma was visible and/or had a complicated course. This implicates the need of special care for children and their parents in case of a visible infantile hemangioma and/or had a complicated course.

To map the complete impact of infantile hemangiomas we reviewed six articles concerning psychosocial impact on infantile hemangiomas in Chapter 8. Small differences in self esteem and feelings of grief are shown, but none of the studies show significant differences between children with and without an infantile hemangioma at older age. There are, however, two exceptions to this conclusion. The first exception is that children with visible infantile hemangiomas tend to have less self-esteem and more psychosocial problems. Although samples are small, they could indicate that psychosocial problems may be related to size and visibility of the infantile hemangioma. The second exception that needs attention is that the parents, acknowledging that their children were too young to appreciate their own condition, had difficulty in coping with their own worries and with reactions from the community. The reactions that parents gave in the hemangioma-related questionnaires indicated that infantile hemangioma in their child has a big impact on them. This resulted from fear, feelings of guilt and, most importantly, negative reactions from family, friends or outsiders. Being accused of child abuse is, unfortunately, an often heard comment. Again visibility is of great importance for these reactions and differences between non-visible and visible hemangiomas were evident. Parents of children with a infantile hemangioma with a complicated course seem to be at risk for more feelings of guilt and fear. This could be explained by the troubles of numerous hospital visits, of seeing their child in pain of an ulcerated infantile hemangioma or worries, e.g. for the vision of the child. Several studies have shown that parents can have major QoL problems related to the illness of their child and this should not be neglected. Again, this implicates special care for children and especially their parents in case of a visible infantile hemangioma and/or had a complicated course.
Chapter 9 comprises a general discussion of hypotheses regarding the etiology of infantile hemangioma in light of the findings presented in the first part of this thesis. Additionally, it includes suggestions regarding the psychological support of parents of children with infantile hemangioma.