A pediatric perspective on Infantile Hemangioma

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Hemangiomen vanuit pediatrisch perspectief

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(met een samenvatting in het Nederlands)

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Serendipiteit

Soms ben je door ons in je wang
jezelf maar in je bloed iemand anders.
Ik wil dat kinderen niet te veel veranderen.
Dat je hoofd blijft en leert onthouden
hoe jong je ook bent.

Dat jij onthoudt hoe je eerste vlinder
eruitzag, dat je kan terughalen
hoe het voelde om je hand
over een vacht te strijken.

Toeval is geen blijvend gevolg, wij
blijven kijken en onderzoeken hoe
we de kluwen vaatjes die aardbeien
maken op je lichaam kunnen bestrijden

zonder dat jij een vlinder verliest.

Voor Martine

Froukje van der Ploeg, mei 2016

Table of contents

Chapter 1

General introduction and outline of the thesis

Infantile hemangiomas (IH) are benign tumors that most often have an uncomplicated course and regress spontaneously. Consequently most IH do not need treatment and a 'wait and see' policy is conducted. Nevertheless some cases of IH cause substantial morbidity and require a more active therapeutic approach. Before any intervention to an infant is initiated, the benefits of the proposed therapy must be carefully weighed against its risks. This introduction provides an overview of past and current clinical care for pediatric patients with IH, with an emphasis on treatment strategies.

Clinical features

IH is the most common benign vascular tumor of infancy (1). In approximately 10% of Caucasian infants IH are seen (2). Premature infants, infants with a low birth weight (< 1500 grams), twins and females are at higher risk of IH development. Normally IH are absent at birth, but usually develop in the weeks and months thereafter. A precursor lesion might be present at birth, such as a small red macula (Figure 1), telangiectasia, or a blue macula (1,3). Hemangiomas are found in all body regions, but occur most often in the head and neck (>60%), the trunk (25%) and extremities (15%) (4). Growth of IH occurs disproportionally for an average period of three to nine months, also known as the proliferation phase (3) and most growth is seen in the first two months (5) (Figure 1). After the proliferation phase a stable period arises, before slow but gradual regression starts. In subcutaneous IH this involution is more delayed, slower and incomplete compared to the superficial lesions (6). After the age of three and a half years, most IH do not show involution anymore (7). While IH can resolve completely, in 69% of all IH residual lesions are found (8).

Fig 1. A red macula at birth and disproportional growth thereafter.

Diagnosis

In most cases the typical natural history and clinical features can make the diagnosis of IH. IH may be classified according to the depth of the lesion being superficial (50-60%), deep (subcutaneous, approximately 15%) or mixed (25-30%) (6,9). A superficial IH presents as a bright red tumor with an irregular surface and is often described as 'strawberry' hemangioma. A subcutaneous IH is a protruding swelling under normal or bluish skin. A mixed IH is a combination of a primary superficial component associated with a subcutaneous extension that occurs later (6).

Furthermore each type is subsequently sub-classified according to size, anatomical localization or morphological subtype, as localized (nodular 67%), segmental (13%), indeterminate (16.5%) or multifocal (3.6%) (6,9,10). The size of an IH may vary greatly, but most often (80%) is less than three centimeters in diameter (10). On palpation IH have a firm and elastic texture and may feel a little warm but do not pulsate. IH are usually painless, except in case of ulceration (6).

Etiology

There are currently three hypotheses that explain IH etiology. The role of local tissue hypoxia has been suggested as triggering signal for the development of IH, since tissue hypoxia seems to be a very powerful inducer of angiogenesis (11). Formation of IH is regarded as a reaction to the hypoxic environment and hemangioma growth as a homeostatic attempt to normalize hypoxic tissue (11). Another proposed mechanism is the embolization of placental endothelial cells that are dislodged into the fetal circulation during gestation, potentially homing to receptive tissues, such as skin and liver (12,13,14). Evidence to support the placental origin theory lies in the increased incidence of hemangiomas in infants whose mothers had undergone chorionic villus sampling (13). This placental hypothesis may explain why IH growth occurs after birth, by the lack of angiogenesis inhibiting factors that are produced by the placenta in utero to prevent proliferation of placental progenitors (14). The final hypothesis on the etiology of IH concerns the stimulation and inhibition of angiogenesis. Intrinsic defects in expression of vascular endothelial growth factor receptor 1 (VEGFR-1) in hemangioma endothelial cells and/or intrinsic activation of VEGF signaling pathways characterize the proliferation phase of IH (15). These endothelial cells also play an important role during the involution phase where they become apoptotic by a yet unknown mechanism (16).

Complications

As stated most IH do not need treatment, but 25% of children with IH have complications and of these over one third need intervention (10). Complications of IH may be classified as being potentially life threatening, causing functional impairment, give rise to local complications (ulceration or bleeding), or may be cosmetic only. In deciding whether to start treatment it is important to take all patient and IH characteristics into account. Presence or risk of complications, the chance of scarring or (permanent) disfigurement and the age of the infant are important factors to consider. Furthermore the growth or involution rate and the size of IH, its morphology (localized/segmental) and its location are characteristics to evaluate while considering initiating treatment (3,17).

Treatment of IH in historical perspective

A range of surgical, interventional and medical treatment options for IH has been described in literature.

Radiation therapy

From 1930 to 1950 irradiation therapy was widely considered an effective treatment of IH (18). Superficial photons and radioactive implants were used for the treatment of IH until the late 1960s (19). Subsequently the risks involved in using ionizing radiation in the treatment of benign disease were demonstrated. Fragu et al., reported that dystrophy occurred 12 times more often in patients who received a surface skin dose > 30 Gy than among those who received a dose of < 10 Gy (20). They also observed basal cell carcinoma of the skin in patients who received > 10 Gy. Furst et al., reported a cancer incidence of 1.46% in patients with hemangiomas that received 5–10 Gy radiation doses, compared with 1.26% in IH patients that were not exposed to radiation, a difference that was not statistically significant (21). In addition, irradiation can cause growth retardation in children as specifically recognized by Gonzalez and Breur who showed that radiation dose to the physeal plates was the most important factor in the shortening of the irradiated extremity (22). These observations demonstrate that when radiation therapy needs to be used to treat life- or function-threatening hemangiomas, the lowest possible dose should be sought after, and the dose to adjacent radiosensitive structures must be < 10 Gy to avoid radiation-induced cancer (19). And only in those cases of life- or function-threatening IH where other treatment options failed, the entire hemangioma can be included in the radiation field.

Corticosteroids

Following radiation, systemic corticosteroids were found to be an effective treatment for IH and since this discovery remained first treatment of choice for a long period. The response rates to steroids vary between 70% and 90% (23, 24). Corticosteroids are thought to inhibit vasculogenesis by silencing expression of vascular endothelial growth factor A (VEGF-A) (25). In contrast, Hasan et al. concluded in an in vitro study with five different corticosteroids that these drugs stimulate apoptosis via the increase of cytochrome B and stimulate the release of anti-angiogenic factors via an increase in mast cells (26). Currently it is known that corticosteroids are useful only when given during the proliferative stage of HIs (27). Systemic corticosteroids are given orally at doses of 2 to 5 mg/kg/day. Treatment effect usually becomes apparent in the second and third week of therapy. If no response (reduction of growth) is observed after two weeks, the corticosteroid dose should be tapered and other therapeutic options should be considered. If there is a good response, the dose is maintained for one to two months and subsequently tapered to the lowest dose that suppresses proliferation for another one to two months. At a patient age of > six months, the likelihood of continued proliferation diminishes and corticosteroids should be tapered as well. Thus, the steroid regimen is primarily used to suppress proliferation until the natural course of involution takes place (27). A rapid decrease in corticosteroid dose may result in rebound of IH proliferation with a possible loss of an already obtained treatment effect (28). Besides varying efficacy, systemic corticosteroids may cause serious side effects that complicate treatment of IH, although these have not been systematically evaluated in large cohorts (29). The well known complications of corticosteroid treatment such as adverse neurodevelopment, aseptic necrosis of the femoral head, growth retardation, diabetes, osteoporosis, adrenal insufficiency, cataracts and glaucoma are associated with high-dose, long-term therapy (30,31). In general these complications have not been observed in patients treated with corticosteroid for IH (29, 32, 33). Short-term side effects of corticosteroid treatment for IH are reversible and may include Cushingoid appearance, sleep disorders, personality change, or gastric irritation. Cutaneous fungal growth and myopathy are rarely reported (29). Approximately one-third of infants exhibit decreased gain in height during corticosteroid treatment, but return to their pretreatment growth curve at two years of age (29). This risk even falls to 12% when patients are treated after three months of age for a period of less than 6 months. Hypertension may be found in some patients but its clinical significance is unclear and it revealed no significant adverse effects (34). Patients receiving corticosteroids for IH are not prone to infections despite a profound yet reversible effect on immune function in this young patient population (35).

Intralesional steroid injections are restricted for the treatment of localized deep proliferating IH when systemic therapy or surgery does not seem appropriate. This approach is especially

useful in the periocular area, where early control of IH of both eyelids and intra orbital IH are important to avoid visual impairment (28). Local injections are usually administered under short general anesthesia and will be repeated at different time points if necessary, with response rates over 70% (36,37). Side effects are limited and mostly local; hypochromia and linear atrophy at the site of injection may occur. Of note, in IH of the periorbital area, serious ocular complications including ophthalmic artery occlusion, retinal embolization and central retinal artery occlusion with a risk of blindness have been reported (28).

Pulsed dye laser

Pulsed dye lasers (PDL) emit light with a vessel-wall coagulation depth of about 0.8 mm and have therefore no impact on deep dermal components. In 1989 PDL became commercially available and was subsequently applied in the treatment of IH. PDL has been used successfully in the treatment of ulcerated IH, where it reduces pain and promotes healing (38). It has also been used to remove the residual telangiectasia. However, the use of PDL in uncomplicated IH is controversial. There are non-randomized studies, which claim that PDL is better than the 'wait and see' policy (39). In a large prospective RCT by Batta et al., children with uncomplicated early hemangiomas were assigned to PDL (585 nm) or observation only (40). After one year there was no significant difference between the two groups in terms of complete clearance or residual lesions. Adverse effects were observed significantly more often in the PDL group, which led the authors to conclude that PDL is no better than observation in uncomplicated superficial IH. In another recent prospective RCT in infants, the intervention group was treated using a longer wavelength (long (L)PDL (595 nm)) (41). The authors did not observe any difference in IH depth or surface area after one year between LPDL and observation only, but did find a significant better cosmetic outcome in the LPDL group. In a comparative study between traditional PDL (585 nm) and LPDL (595 nm), a similar number of infants achieved complete clearance or showed minimal residual signs at one year of age, although the infants in LPDL group suffered from significantly less side effects like hypo- or hyperpigmentation or textural changes. In addition, the period of maximal proliferation was significantly reduced in the LPDL group (42). In general PDL treatment is painful and as a result anesthesia plays an important role in treating the pediatric patient with IH. Preferably noninvasive local anesthesia methods, such as topical anesthetics can be used but if a young child is unable to cooperate with the procedure, general anesthesia may be needed. There is no consensus on the optimal settings of PDL nor which type of hemangiomas are the most suitable for PDL treatment. Currently, the use of PDL is confined to the treatment of ulceration and post-involution erythema and telangiectasias (43).

Immune modulator therapy

Interferon alpha

Interferon alpha was first reported as a novel therapy for IH in 1991, but is associated with serious neurotoxicity (44, 45). Interferon alpha is an anti-angiogenic agent that decreases proliferation of endothelial cells by downregulation of beta-fibroblast growth factor (b-FGF) or interleukin (IL)-8 and the VEGF gene expression (46, 47, 48). It is indicated in complicated IH not responding to any other treatment. Interferon alpha dose varies from 1 to 3 million units/m^2/day administered by subcutaneous injection. Duration of the treatment is long and may vary from six to twelve months. A complete response rate of 40–50% has been reported with first signs of regression appearing after two to twelve weeks (45,49). Side effects are common with fever and muscle aches (flu-like symptoms), especially at start of treatment. Other side effects have been reported such as hepatic and hematological toxicity, hypothyroidism, fever, fatigue, hair loss, depression, but also gastro-intestinal and metabolic disturbances. Of note, severe neurotoxicity with spastic diplegia and developmental delay has been reported in 10–30% of cases (50).

Imiquimod

Topical imiquimod is known to influence the immune system by induction of cytokine synthesis and thereby stimulating secretion of cytokines from macrophages, monocytes and keratinocytes in the epidermis. These cytokines, interferon, tumor necrosis factor alpha (TNFa) and ILs lead to a reduction of pro-angiogenic factors, to cell death in endothelial cells and to a decreased vascular invasion and motility (51). Adjacent, IL-12 can inhibit angiogenesis in vivo and tube formation of endothelial cells in vitro (52). Therefore, the mechanism of action of imiquimod is ascribed to a cascade that results in the synthesis of cytokines that inhibit growth of IH (53). Imiquimod cream can be used three to seven times a week for several months. Side effects reported were both local skin reactions and systemic symptoms of fever and gastro-intestinal complaints.

Sirolimus

Mammalian target of rapamycin (mTOR) acts as a master switch for numerous cellular processes including angiogenesis and cell growth (54). Sirolimus is a mTOR inhibitor and could therefore be beneficial in the treatment of vascular anomalies (55). It is also seen as a temporizing proliferator of endothelial glucose transporter-1 (GLUT1) selected cells and GLUT1 is a diagnostic marker for IH (56). Sirolimus can be given orally and adequate plasma level ranges from 9 - 12 ng/ml. Given the potential risk of immunosuppression during long term treatment, pneumocystis prophylaxis is advised. Several side effects and adverse events such as hypertriglyceridemia, (febrile) neutropenia and mild mucositis are reported (57).

Chemotherapy

Vincristine

Vincristine is an anti-angiogenic agent that interferes with mitotic microtubules and induces apoptosis of tumor cells in vitro (58). It is indicated in severe complicated IH not responding to corticosteroids. Treatment modality includes a weekly intravenous administration of 0.05 mg/kg or 1 mg/m^2 for at least 15 weeks. Efficacy rate is nearly 100%, with regression of the hemangioma, beginning usually three weeks following treatment initiation. Side effects may include fatigue, alopecia, constipation, abdominal pain, jaw pain, peripheral neuropathy, hematological toxicity and inappropriate secretion of antidiuretic hormone.

Bleomycin

Bleomycin is a cytotoxic agent, which degrades deoxyribonucleic acid (DNA), resulting in an inhibition of cell replication, cell growth and DNA-synthesis (59). It is used as an intralesional treatment for IH (60). This sclerosing agent acts on vascular endothelium by induction of cell-injury and disperse endothelial cells, leading to occlusion of blood vessels. Overall, it stimulates apoptosis of rapidly dividing cells, as is seen in proliferating IH. Dose and frequency of injection differ per protocol. Side effects and adverse events consist of local symptoms at the injection site, but also systemic gastro-intestinal complaints are reported.

Cyclophosphamide

Cyclophosphamide is an alkylating agent affecting DNA and the cell cycle process. It is known for its immunosuppressive effect on B- and T-cells. Dose and frequency of intravenous administration differ per protocol. One patient with diffuse neonatal hemangiomatosis was treated with cyclophosphamide, but suffered from fever, sepsis, catheter infection and hypertension (61).

Surgery

Surgical treatment, like debulking or complete resection, includes early and late interventions with different indications and outcomes. Early surgery during the growth phase, may be considered in certain types of IH: well-localized function-impairing IH not responding to medical treatment, IH without significant regression in size after 8 to 12 months, as well as IH with persistent bleeding or ulceration (62). The main risk of surgery is residual scarring, which should always be taken into account when weighed against a 'wait and see' policy. Late surgery following regression of IH is sometimes needed. It aims to

repair post-regression cutaneous (atrophic wrinkling, discoloration, redundant skin fibro-fatty residual tissue) and anatomical consequences. Late surgery may be combined with laser treatment for residual telangiectasias.

Beta-blokker therapy

Propranolol

In 2008 the efficacy of propranolol, a non-selective beta-blocker, in IH was discovered by accident (63). In two children propranolol treatment was started because of cardiac complications due to the treatment with systemic corticosteroids. Proliferation of IH stopped and an early and rapid involution was observed next. Since then, many others reported equally favorable effects of propranolol treatment in IH, even when initiated after the proliferation phase or in ulcerated IH. Hogeling et al. performed the first randomized controlled trial (RCT) with propranolol (64). They reported that propranolol when administered orally at 2 mg/kg/day, reduced volume, color, and elevation of both focal and segmental IH in infants younger than six months and children up to five years of age compared to the placebo group. Another randomized trial by Léauté-Labrèze et al., showed that propranolol was effective at a dose of 3 mg/kg/day for six months in the treatment of infantile hemangioma compared to placebo or other propranolol treatment schemes (65). Propranolol is now considered as the first line therapy for IH. Propranolol is a lipophilic, non-selective beta-blocker that was released in 1964. Ever since, propranolol has been used widely in pediatric cardiology. The mechanism by which propranolol has an effect on IH is not completely understood, but it is thought to originate from vasoconstriction of capillaries. This causes discoloration and softening of the tumor as well as decreased expression of VEGF and FGF leading to a decrease of proliferating endothelial cells (66,67). Furthermore propranolol induces apoptosis of capillary endothelial cells by blocking IH Glut-1 receptors and inhibits the expression of angiogenic extracellular matrix degrading proteinase (MMP-9) and human brain microvascular endothelial cells (HBMEC), which may result in an anti-angiogenic effect (68,69). These mechanisms involve the beta-2 receptor blockade pathway (66,69). Itinteang et al., suggested that propranolol may also act via inhibition of renal beta-1 receptors, leading to suppression of the renin-angiotensin-aldosterone system (RAAS) by reduction of renin activity and thereby decreasing the conversion of angiotensinogen to angiotensin I and finally to angiotensin II (70). This, together with a reduction of the VEGF concentration, causes inhibition of proliferating CD34+/VEGFR-2 endothelial progenitor cells in the capillaries of proliferating IH. Finally there may be current unknown mechanisms through which beta-blockers mediate their effect on IH. Due to beta-2 receptor blockade propranolol is associated with several side effects. The most common side effects are hypotension, bradycardia, hypoglycaemia,

bronchial hyperreactivity, cold extremities, sleep disturbances and diarrhea (64,71,72,73). There is more concern, as in adults a reduction in subsequent memory for both new and previously learned emotional material and an impairment of mood and sleep quality was reported following propranolol use (74, 75). In addition a retrospective survey in families of children treated with oral propranolol for IH on gross motor development revealed a statistically significant delay in walking unassisted when compared to children taking other medications (76).

Outline of this thesis

There is a clear need to optimize care and treatment for IH in children. Although IH is the most common benign vascular tumor of infancy it is important to obtain a proper diagnosis of complicated IH. As only a minority of IH patients will require therapy careful clinical judgment is warranted before treatment is initiated. Physicians with experience in IH should determine the indication for any kind of intervention. The studies presented in this thesis aim at further optimization in care and treatment for IH in children.

Part I reflects current medical treatment strategies in IH. There is no doubt that the discovery of the efficacy of beta-blockers has had a profound impact on IH treatment and outcome. Though, we encountered several adverse effects from propranolol therapy in our IH patients as well, as described in Chapter 2. In Chapter 3 we report a good clinical response to atenolol treatment in two patients with complicated IH, after adverse effects prompted us to discontinue propranolol therapy. Chapter 4 describes the efficacy and side effects of the treatment with atenolol compared to a historical cohort treated with propranolol.

The second objective of this thesis was to evaluate the current treatment guideline for children with IH from a pediatric point of view. The outcomes of these studies are described in part II. While the consensus guideline with recommendations for treatment of IH with propranolol was formulated (77), the clinical relevance of certain baseline assessments and monitoring remained unclear. In order to address these issues we studied cardiovascular data from all our patients with IH treated with beta-blockers as reported in Chapter 5. Next, in Chapter 6, a review of therapeutic options for IH in children is presented to provide a more safe and optimal treatment and monitoring approach.

The studies in the third part of this thesis concern how to achieve best possible care for a subgroup of rare pediatric vascular lesions. In Chapter 7 we determined the prevalence of PHACES syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects, Eye anomalies, Supraumbilical raphe and/or Sternal pit) in patients

with obstructive aortic arch pathology (OAAP) in order to achieve more insight in the possible association between IH and cardiovascular anomalies. In Chapter 8 we report a case of a prenatally diagnosed vascular congenital tumor, which reached maturity in utero. And Chapter 9 is an evaluation of literature for therapeutic options for kaposiform hemangioendothelioma (KHE) with and without Kasabach-Meritt phenomenon (KMP) and we compared therapy used in Dutch KHE patients with the proposed treatment plan of a consensus meeting.

During the course of the studies described in this thesis novel insights were obtained regarding future care and treatment for IH in children. These are discussed in an integrated manner in Chapter 10. Chapter 11 provides the summary of this thesis.

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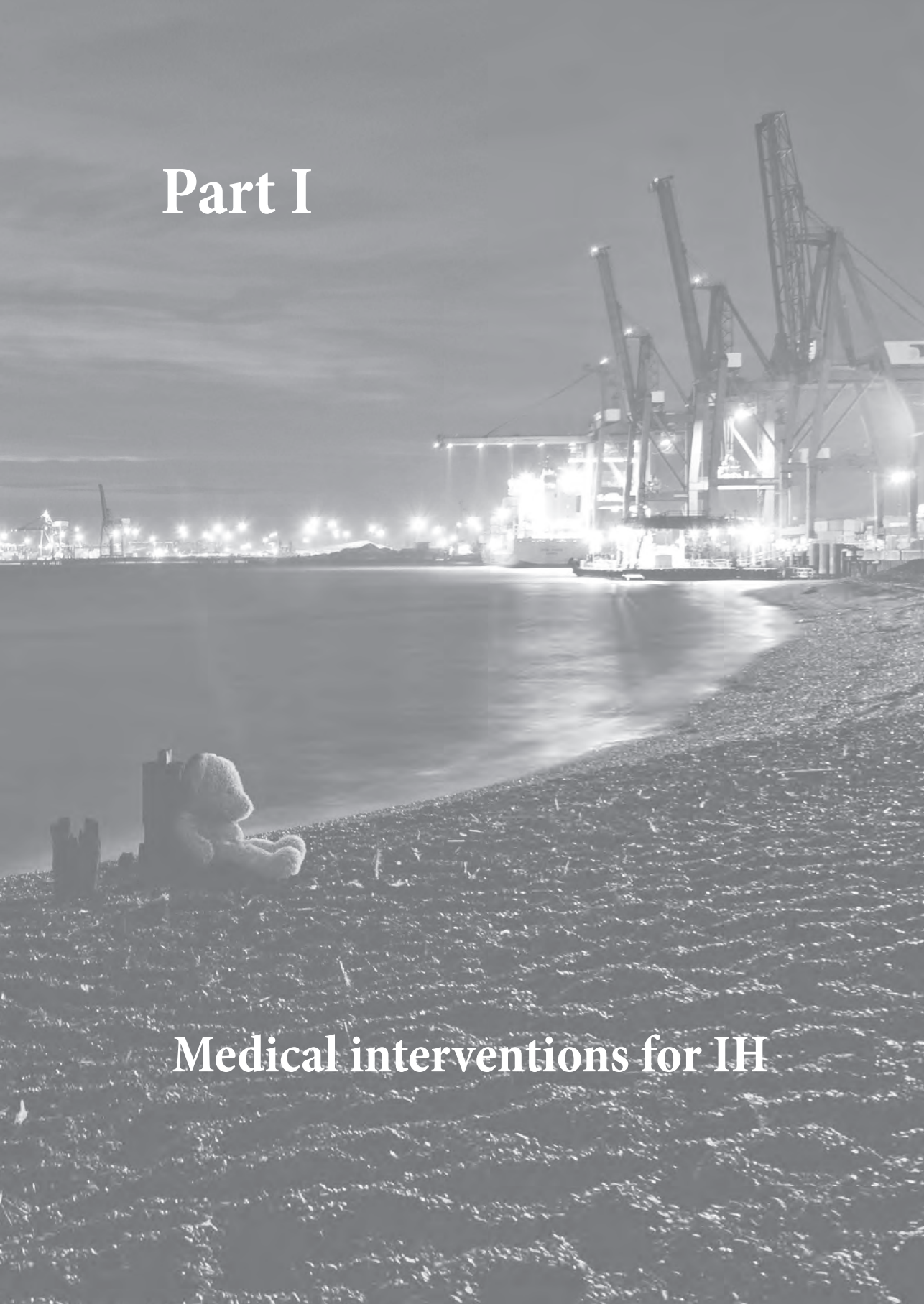

Part I

Medical interventions for IH

Chapter 2

Adverse effects of propranolol when used in the treatment of hemangiomas: A case series of 28 infants

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Abstract

Background Infantile hemangioma (IH) is a frequently encountered tumor with a potentially complicated course. Recently, propranolol was discovered to be an effective treatment option.

Objective To describe the effects and side effects of propranolol treatment in 28 children with (complicated) IH.

Methods A protocol for treatment of IH with propranolol was designed and implemented. Propranolol was administered to 28 children (21 girls and 7 boys, mean age at onset of treatment: 8.8 months).

Results All 28 patients had a good response. In two patients, systemic corticosteroid therapy was tapered successfully after propranolol was initiated. Propranolol was also an effective treatment for hemangiomas in 4 patients older than 1 year of age. Side effects that needed intervention and/or close monitoring were not dose dependent and included symptomatic hypoglycemia (n = 2; 1 patient also taking prednisone), hypotension (n = 16, of which 1 is symptomatic), and bronchial hyperreactivity (n = 3). Restless sleep (n = 8), constipation (n = 3), and cold extremities (n = 3) were observed.

Limitations Clinical studies are necessary to evaluate the incidence of side effects of propranolol treatment of IH.

Conclusions Propranolol appears to be an effective treatment option for IH even in the nonproliferative phase and after the first year of life. Potentially harmful adverse effects include hypoglycemia, bronchospasm, and hypotension.

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Introduction

Infantile hemangiomas (IH) are benign vascular tumors found in approximately 4% to 10% of white infants.[1] They are characterized by a 3- to 9-month period of rapid growth followed by gradual involution.[2] Historically, prednisone has been used for treatment of complicated IH.[3] However, systemic steroid therapy is associated with numerous potentially serious side effects, including hypertension, growth retardation, intracranial hypertension (when tapering prednisone), osteoporosis, immunosuppression, and a cushingoid appearance.[4] Recently, Léauté-Labrèze et al[5] reported a spectacular response to treatment of IH with propranolol, and this was confirmed in other studies.[6-13]

We describe the results of propranolol treatment and associated side effects in 28 patients with IH.

Patients and methods

Propranolol treatment was administered to 28 children with IH associated with life-threatening potential, functional risk, local complications, or cosmetic disfigurement. A treatment guideline was designed that was based on the known side effects of propranolol and in collaboration with pediatric cardiologists, hematologists, dermatologists, and plastic surgeons. Children younger than 1 month of age and those at risk for development of hypoglycemia, bradycardia and/or hypotension, or infants with other relative contraindications to propranolol were treated in an inpatient clinic (Figure 1). All other children were treated as outpatients.

Before treatment was started, an electrocardiogram (ECG) was performed to detect any preexisting cardiac conduction disturbance. Serial photographs of the IH were obtained to evaluate the efficacy of propranolol. The starting dosage was 1 mg/kg/day in 2 or 3 divided daily doses. The dosage was increased to 2 mg/kg/day after a minimum of 5 doses, since stable plasma concentrations of propranolol are established at that time. During treatment the dose was adjusted for increase in weight. In cases in which the clinical response was inadequate, the dose was increased stepwise to 4 mg/kg/day.

Following uneventful introduction of propranolol, inpatients were discharged home on day 5 (or after 10 doses). Outpatients were evaluated after 1, 2, 4, 8 and 12 weeks. At each clinic visit, blood pressure and heart rate were measured, the effect of the treatment was determined, and possible adverse events were documented.

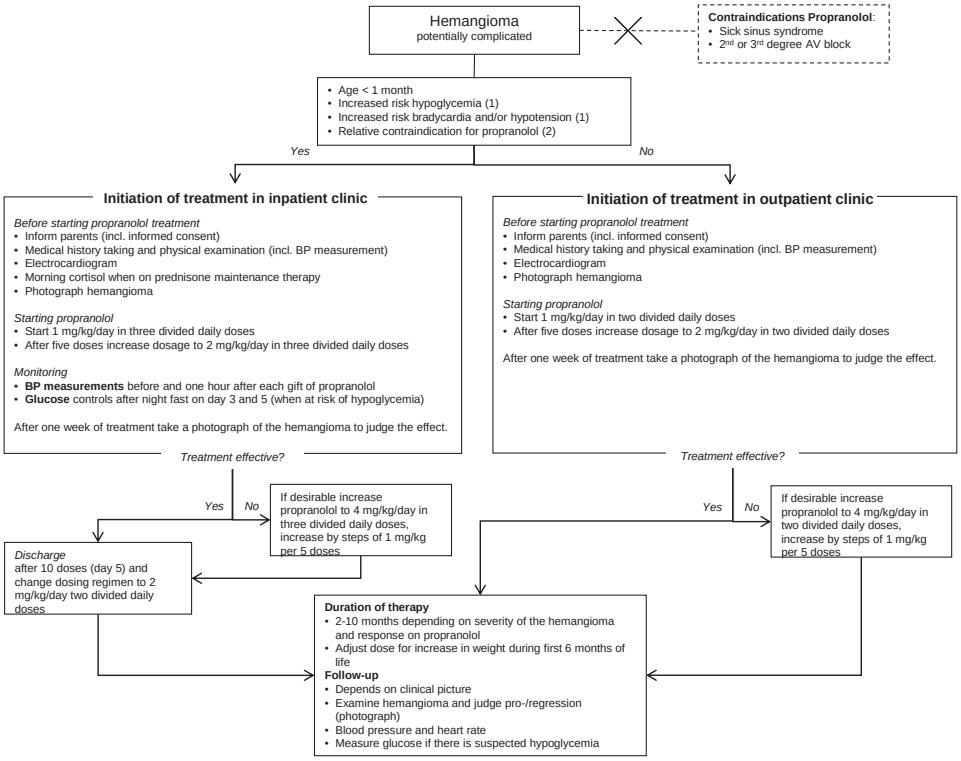

Fig 1. Guidelines for utilization of propranolol in the treatment of (complicated) IH at Wilhelmina's Childrens Hospital. (1) For example, prematurity or dysmaturity and/or simultaneous use of prednisone; (2) Relative contraindications to propranolol: impaired cardiac function (when this is secondary to the hemangioma, appropriate treatment is advisable); sinus bradycardia, hypotension, first-degree atrioventricular block, asthma, and/or bronchial hyperreactivity, diabetes mellitus, chronic renal insufficiency. AV, Atrioventricular; BP, blood pressure.

Results

Patients

Of the 28 patients treated with propranolol, 21 (75%) were female and 7 (25%) were male. One patient had PHACE (Posterior fossa abnormalities, Hemangiomas, Arterial abnormalities, Cardiac anomalies, Eye abnormalities) syndrome; magnetic resonance angiography showed malformations of the cerebral arteries (occlusion of the left internal carotid artery and left vertebral artery, and stenosis of the right internal carotid artery with a dilatation in the neck). Another patient had LUMBAR (Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformaties, Anorectal malformations and Arterial anomalies, and Renal anomalies) syndrome. Two patients

were previously treated with oral prednisone, 4 with intralesional corticosteroids, 1 with intravenous vincristine, 1 with pulsed dye laser therapy and 1 by surgical debulking of the hemangioma before receiving propranolol. No significant ECG abnormalities were reported.

The median age at the time of initiation of propranolol treatment was 6 months (range, 2 to 43 months). The location of the IH and other details are listed in Table 1.

Effects of treatment with propranolol

A rapid improvement of the IH was observed in every patient. After 1 week all lesions had changed in color from bright red to purple with areas of gray. Considerable softening to palpation was noted. After a remarkable initial response to treatment, the IH continued to regress with respect to both color and thickness.

The maximum dosage of propranolol varied between 1.8 and 4 mg/kg/day. In patients 1, 4, 5, 9, 10, and 20, the duration of treatment varied between 4.5 and 17 months. The remaining patients were still receiving propranolol treatment at the time of writing.

Side effects of treatment of IH with propranolol

Observed side-effects ranged from mild to severe (see Table 1).

Hypoglycemia (n = 2). Patient 4 (Figure 2) had a rapidly growing segmental facial IH obstructing vision and hearing. There was a rapid response to treatment with prednisone 4 mg/kg per day, which was started shortly after birth. Several attempts to taper the dose of prednisone failed because of rebound growth. Propranolol (2 mg/kg/day) was introduced at age 15 months following which prednisone was tapered successfully. Four days after the dose of prednisone was reduced to 0.1 mg/kg/day, her mother found her unresponsive in bed. Blood glucose, measured by paramedics, was 1.7 mmol/L. After a yoghurt drink, the patient became fully alert. The dose of prednisone was increased. Several days later, another hypoglycemic event occurred (blood glucose 1.9 mmol/L). The morning serum cortisol level was found to be undetectable (<0.2 μmol/L) as a result of iatrogenic adrenal insufficiency. Cornstarch in yoghurt at bedtime was given to prevent future hypoglycemic events. Oral prednisone was tapered to 0.05 mg/kg/day and continued until the morning serum cortisol was greater than 0.3 μmol/L. The propranolol dosage was reduced as well, but shortly afterwards the IH showed rebound growth. The original dose (2 mg/kg/day) was resumed without a recurrence of hypoglycemia.

Patient 13 suffered from pathological food refusal. While taking propranolol for treatment of IH, she was hospitalized for a hunger provocation test to increase her motivation to eat in a controlled fashion. After a prolonged period of fasting, she became less responsive and the serum glucose was 2.7 mmol/L. Propranolol was discontinued for the remaining duration of the hunger provocation test.

Table 1. Clinical characteristics of the 28 patients*

Patient	Gender	Location of IH	Indication for propranolol	Previous treatment	Age at initiation of propranolol treatment [months]	Age at end of propranolol treatment [months]	Side effects	Maximum dosage propranolol (mg/kg)	Blood pressure before treatment (systolic/ diastolic)	Lowest measured blood pressure during treatment (systolic/ diastolic)
1	F	Face (large segmental IH) PHACE syndrome	functional/ rebound prednisone	prednisone	11	28		2.5	96/56 (p50=54)	85/**33** (p50=55)
2	M	Face (periocular area)	functional		5	t	restless sleep, constipation	2		80/**44** (p50=52)
3	F	Face (large segmental IH)	functional	surgical debulking	43	t	Paleness; no muscle tone w/o hypoglycemia	2		92/**50** (p50=57)
4	F	Face (large segmental IH)	functional/ rebound prednisone	prednisone	15	21	hypoglycemia while on propranol and prednisone	2	128/78 (p50=55)	94/63 (p50=55.5)
5	F	Genitals (LUMBAR syndrome)	functional		2.5	14		3		91/64 (p50=53)
6	M	Upperlip and nose	functional		11	t		2	98/61 (p50=51)	86/56 (p50=56)
7	F	Subglottis	functional	intralesional corticosteroids	2.5	t	symptomatic hypotension, reduced intake, vomiting	1.8	120/65 (p50=51)	56/**34** (p50=53)
8	F	Upper eyelid	functional		2	t		3.8	93/47 (p50=51)	84/**46** (p50=50.5)
9	F	Upper eyelid	functional		6.5	11	bronchial hyperreactivity, constipation	2.2	105/65 (p50=52.5)	88/**50** (p50=53)

Table 1. Clinical characteristics of the 28 patients* *(Continued)*

Patient	Gender	Location of IH	Indication for propranolol	Previous treatment	Age at initiation of propranolol treatment [months]	Age at end of propranolol treatment [months]	Side effects	Maximum dosage propranolol (mg/kg)	Blood pressure before treatment (systolic/ diastolic)	Lowest measured blood pressure during treatment (systolic/ diastolic)
10	F	Nose	functional		6	14	constipation	2		74/**37** (p50=54) (during sleep)
11	F	Subglottis	functional/ stridor	intralesional corticosteroids	6	t		2	128/68 (p50=52)	74/**46** (p50=54)
12	M	Upper lip	functional		6	t		3.5	114/64 (p50=53)	84/**54** (p50=55.5)
13	F	Face, neck, thorax, arm	functional	vincristine	32	t	hypoglycemia during reduced intake, restless sleep, nausea	4	90/60 (p50=57)	92/**49** (p50=57)
14	F	Forehead, neck, thorax	functional		7	t	restless sleep	3	121/49 (p50=53)	88/59 (p50=53)
15	F	Cheek, scalp, thorax	cosmetic		19	t	restless sleep	2.4	100/70 (p50=55)	81/**53** (p50=55)
16	F	Eye, ear, thorax	functional	laser	3	t		2.2		60/**34** (p50=51)
17	F	Nose, thorax, shoulder	functional		7	t		2.3	111/69 (p50=53)	88/52 (p50=53)
18	M	Face (parotid area)	functional	intralesional corticosteroids	7	t	malaise	1.9	98/57 (p50=54)	82/**42** (p50=54)
19	F	Subglottis	functional/ stridor	intralesional corticosteroids	2	t	cold extremities	2	74/56 (p50=51)	94/68 (p50=51)

Table 1. Clinical characteristics of the 28 patients* *(Continued)*

Patient	Gender	Location of IH	Indication for propranolol	Previous treatment	Age at initiation of propranolol treatment [months]	Age at end of propranolol treatment [months]	Side effects	Maximum dosage propranolol (mg/kg)	Blood pressure before treatment (systolic/ diastolic)	Lowest measured blood pressure during treatment (systolic/ diastolic)
20	F	Ear (external acoustic meatus)	functional		4	8		2.2		100/**43** (p50=52)
21	F	Upper lip	functional		4	t	restless sleep	2.5	133/73 (p50=51)	72/**36** (p50=52.5)
22	M	Lower lip, chin	functional/ diagnostic		6	t	restless during day and night	2.3		100/56 (p50=54)
23	F	Lower lip	functional		9	t	restless sleep, reduced intake	2		61/**49** (p50=54)
24	F	Genitals	functional/ ulceration		8	t		2.2	88/51 (p50=53)	89/76 (p50=55)
25	F	Face (cheek)	diagnostic		10	t		1[a]	107/67	125/65[b]
26	F	Forehead, right foot	functional		3	t	cold extremities	1[a]	100/65	91/76[b]
27	M	Forehead, abdomen	cosmetic		6	t	bronchial hyperreactivity, cold extremities, restless sleep, diarrhea	1[a]	107/65	85/51[b]
28	M	Nose	functional		3	t	bronchial hyperreactivity	1.8	115/74	75/52[b]

F, Female; IH, infantile hemangioma; M, male; p50, 50th percentile of diastolic blood pressure (diastolic blood pressure level at midpoint of normal range) corrected for age and gender; PELVIS (syndrome), perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, skin tag; PHACE (syndrome), posterior fossa abnormalities, hemangioma, arterial abnormalities, cardiac anomalies, eye abnormalities; t, receiving treatment. Bold typeface indicates that diastolic blood pressure was below p50.

*Propranolol was administered to 28 children with an IH associated with functional risk (eg, impediment to hearing, breathing, and/or eating), local complications (eg, ulceration), rebound growth of the IH after tapering the dose of prednisone, or cosmetic disfigurement. In two patients, propranolol treatment was started to differentiate between an IH and a vascular malformation.

a Just initiated propranolol treatment.

b Blood pressure measured only once because of recent initiation of propranolol treatment.

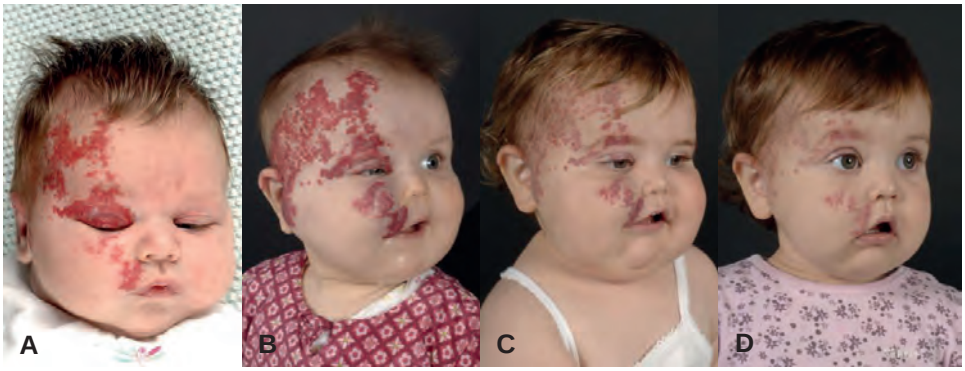

Fig 2. Patient 4. A, Age 4 weeks, no treatment. B, Age 33 weeks, after the first course of prednisone treatment had been stopped. C, Age 15 months, 3 weeks after starting propranolol. D, Age 18 months, during propranolol treatment. Published with the permission of parents.

Bronchial hyperreactivity (n = 3). Patients 9, 27, and 28 suffered from bronchial hyperreactivity associated with a viral infection after initiation of propranolol. None had a history of bronchial hyperreactivity. Propranolol was discontinued in all 3 patients with rapid resolution of wheezing. In patients 27 and 28, propranolol was successfully restarted afterwards.

Hypotension (n = 16, of which 1 is symptomatic). During a routine clinic visit, patient 7 was observed to have very cold extremities with prolonged capillary refill. Her blood pressure was 56/34 mmHg (50th percentile [p50] for diastolic blood pressure at age 7.5 months = 53 mm Hg). Because of this low blood pressure, the propranolol dosage was maintained below 2 mg/kg/day. Most patients showed a decrease in blood pressure; 16 of 28 patients had a diastolic blood pressure below p50 (see Table 1), but only patient 7 had symptoms possibly attributable to hypotension. Propranolol dosage was not adjusted in asymptomatic patients.

Seizure. Five hours after the first dose of propranolol, patient 5 had a staring spell and tonic-clonic movements of her arms and legs. She was unresponsive to her parents during this incident. After 3 minutes she recovered spontaneously. Paramedics transported her to a local hospital where neither the blood pressure nor serum glucose was measured. An electroencephalogram was not performed. Propranolol was restarted while patient 5 was an inpatient at our hospital without further adverse events.

Other side-effects. Parents reported restless sleep in 8 infants (29%), constipation in 3 (11%), and cold extremities in 3 patients (11%).

Discussion

Efficacy

Propranolol is a lipophilic, nonselective beta-blocker, available since 1964 and widely used in pediatric cardiology. There has been limited experience of propranolol for treatment of IH and the mechanism of action is poorly understood.[5,6] The therapeutic effect is thought to originate from a vasoconstrictive effect on the capillaries in IH. Propranolol also decreases expression of vascular endothelial growth factor and fibroblast growth factor and induces apoptosis of capillary endothelial cells.[6,8,14] Another postulated mechanism is that beta-blockers may induce apoptosis by blocking IH GLUT-1 receptors.[7]

Propranolol was an effective treatment for IH in 4 infants over 1 year of age (patients 3, 4, 13, and 15). Propranolol, started at age 11 and 15 months respectively, allowed successful withdrawal of prednisone in two steroid-dependent infants (patients 1 and 4) with progressive regression of the IH.

Treatment of patient 1 and another child with PHACE syndrome, reported previously, suggests that propranolol may be used in patients at risk for cerebral ischemia due to abnormal cerebral vasculature.[8] Careful clinical observation with frequent blood pressure measurement until stable serum concentrations of propranolol are established is obviously warranted in these children.

Side-effects

Symptomatic hypoglycemia can be a serious complication of propranolol treatment. Nonselective beta-blockers are competitive antagonists of catecholamines at the beta-1 and beta-2 adrenergic receptors. Beta-2 receptor blockade may result in hypoglycemia as a result of decreased glycogenolysis, gluconeogenesis, and lipolysis. Patients taking propranolol may be vulnerable to hypoglycemia during periods of prolonged fasting when counter-regulatory mechanisms may fail. As a result of beta-1 blockade, signs of hypoglycemia such as tachycardia, sweating, and anxiety may be absent.[15]

Although there are no documented cases of serious cardiovascular morbidity or mortality from propranolol,[16] a number of cases of hypoglycemia during periods of restricted oral intake have been reported. Most concern long preoperative fasts.[17-21] A propranolol dosage of over 4 mg/kg/day seems to put the pediatric patient at risk for development of hypoglycemic events.[17,18,20,22,23] However, hypoglycemia in patients 4 and 13 appeared to be unrelated to the dose of propranolol.

Patient 4 had a normal oral intake, and additional testing of blood and urine was negative for disorders of carbohydrate or fatty acid metabolism. Undetectable morning cortisol levels were most likely due to adrenal insufficiency from prednisone therapy. When the blood glucose is low, counter-regulatory hormones (glucagon, growth hormone,

cortisol, and epinephrine) act in concert by increasing blood glucose concentrations.[24] When a concurrent deficiency of several hormones exists (epinephrine by beta-blockade and cortisol by adrenal insufficiency), hypoglycemia may occur, especially during episodes of fasting. Therefore extreme care should be taken when propranolol is initiated in patients receiving corticosteroid therapy.

Propranolol treatment was associated with a decrease in blood pressure. One patient experienced cold extremities and a prolonged capillary refill time. However, serious sequelae suggestive of organ hypoperfusion (such as loss of consciousness) due to hypotension were not reported.

One patient probably experienced a seizure after the first dose of propranolol. A possible explanation for this seizure could be hypoglycemia, but diagnostic investigations were not performed. Hypoglycemia has never been reported in healthy infants at the propranolol dosage used in this case. The fact that propranolol was restarted without any adverse effects makes a causal relationship between propranolol and the seizure-like incident highly unlikely.

In 11% of patients (3/28), propranolol had to be discontinued due to bronchial hyperreactivity during viral infections. Bronchial hyperreactivity is a direct effect of non-beta selectivity of propranolol, resulting in bronchospasm due to pulmonic beta2-blockade. The use of a non-selective lipophilic beta-blocker results in several other reported side effects. Restless sleep probably is a direct result of the lipophilic character of propranolol, which allows it to cross the blood brain barrier.25

Previous reports of propranolol treatment of IH did not comment on or reported limited side effects.[5-13] A possible explanation for this difference may be our multidisciplinary approach in which patients are frequently evaluated and closely monitored in the outpatient clinic by a pediatrician, a pediatric dermatologist, and/or a pediatric plastic surgeon. However, information from a case series has limitations and further clinical studies are necessary to determine the incidence of these adverse effects.

A solution to many of the side effects of propranolol therapy may be the use of more selective beta-1 antagonists such as metoprolol, which, at low dosage, have little beta-2 activity; thus, in theory, they bear a lower risk of inducing hypoglycemia and bronchospasm. Treatment with a hydrophilic beta-1 antagonist such as atenolol may prevent side effects, such as restless sleep. However, it is not yet known if these selective beta-blockers will have efficacy that is equal to propranolol.

Our study confirms the impressive results of propranolol as a treatment for IH. It seems to be a more effective and safer therapeutic drug than systemic corticosteroids. Its use may be expanded to treatment of IH after the first year of life. Because of potentially harmful side effects, including hypoglycemia, bronchospasm, and hypotension, these patients are preferably treated in a multidisciplinary setting by physicians knowledgeable about the effects and side effects of propranolol.

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Chapter 3

Atenolol: A promising alternative to propranolol for the treatment of hemangiomas

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Letter to the editor

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In this issue of the Journal, we report our experience with propranolol as an effective treatment for infantile hemangiomas (IH).[1] Despite the good results, two patients had to discontinue propranolol treatment because of adverse effects. We hypothesized that the use of a hydrophilic, selective beta-1 blocker could avoid these side effects. We present the preliminary results of the first patients treated with atenolol for IH.

Patient 1 presented with a nose tip IH (Cyrano nose) for which propranolol treatment was started at age 3 months. Because of severe bronchial hyperreactivity necessitating hospital admission for oxygen therapy and bronchodilator medications and because of hypotension with diastolic blood pressure around the fifth percentile for age, propranolol was repeatedly discontinued and dosage could not be raised to 2 mg/kg per day. During propranolol treatment, an improvement in volume and color was observed. At age 9 months, treatment with atenolol was started (first 7 days 0.5 mg/kg per day, thereafter 1 mg/kg per day). Atenolol was well tolerated and no bronchial hyperreactivity occurred. Blood pressures remained above the 50th percentile. The hemangioma responded to atenolol (Figure 1) and is currently in regression after 2.5 months of therapy.

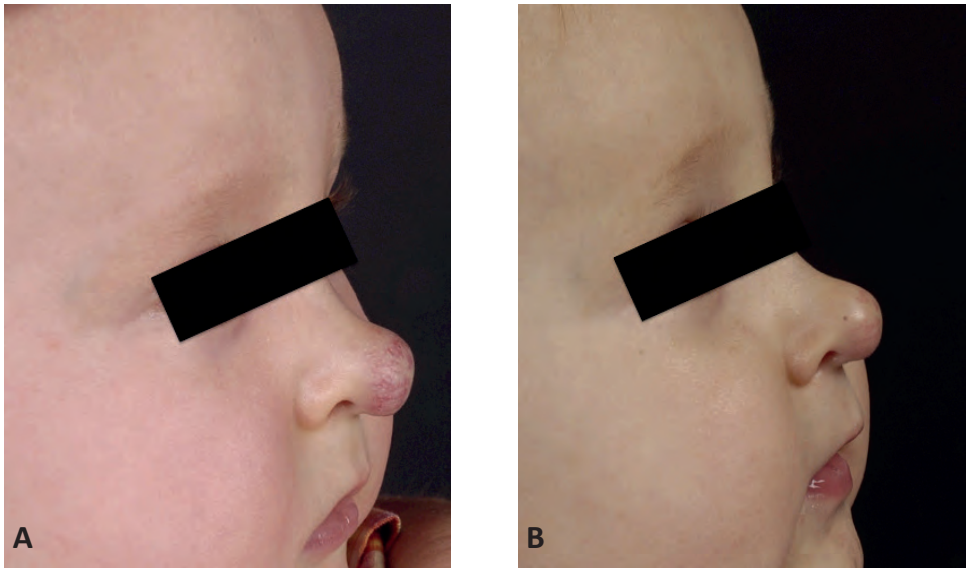

Fig 1. A, One month after stopping propranolol treatment and at start of atenolol treatment.
B, 2.5 months after starting atenolol treatment.

Patient 2 is a 3½-month-old boy with an ulcerating sacral hemangioma for which ulcer excision was performed and propranolol treatment initiated. During propranolol treatment the boy had problems falling asleep and was restless while sleeping. Discontinuation of propranolol resulted in a normal sleeping pattern. At age 5 months propranolol was restarted at a lower dose of 1 mg/kg per day. The hemangioma responded well, but the side effects reoccurred. Sleep disturbance responded well to cessation of propranolol. Atenolol was subsequently started at age 9 months (first 7 days 0.5 mg/kg per day, thereafter 1 mg/kg per day). No side effects occurred. Follow-up at the age of 10½ months showed further regression of the hemangioma (Figure 2).

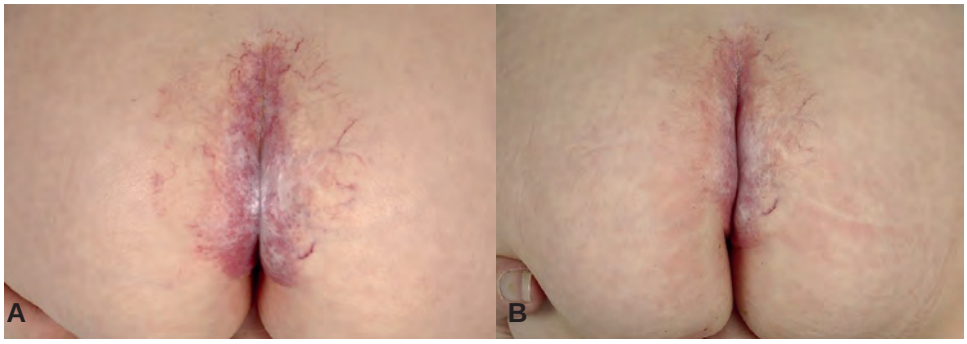

Fig 2. A, One month after stopping propranolol treatment and 1 week before start of atenolol treatment. Scars after excision of ulceration are visible. **B**, One month after start of atenolol treatment.

Propranolol, a lipophilic nonselective beta blocker, has been introduced as an effective treatment for IH.[2] The effect of propranolol might be attributed to beta-2 blockage in the endothelial cell resulting in vasoconstriction, inhibition of angiogenesis, and induction of apoptosis.[3] Despite excellent results, we observed serious side effects.[1] We hypothesized that the use of a hydrophilic beta-1 antagonist could avoid the adverse events observed during propranolol therapy. Hydrophilic beta blockers, which appear at low concentrations in brain tissue, are less likely to produce central nervous system-related side effects (nightmares and hallucinations) than lipophilic beta-blockers, which occur at higher concentrations in the brain.[4] In addition, atenolol is less likely to produce pulmonary side effects.[5]

Therefore atenolol was started during hospital admission in two patients who had to discontinue propranolol due to side effects. Follow-up visits for effects and side effects were frequently performed by experienced dermatologists and pediatricians in the outpatient clinic. These visits included obtaining medical history and physical examination with monitoring of blood pressure and heart rate. Serum glucose values were obtained during the first week of treatment. Both patients tolerated atenolol very well and no adverse events

occurred. Furthermore, the hemangiomas responded well on atenolol therapy, although maybe slightly slower, as seen in patient 1.

A possible explanation for the observed effect is the limited beta-2 blocking potential of atenolol.[6] This may also explain why the spectacular discoloration of the IH in the early phase of therapy (early vasoconstriction) was not observed.[7] Another explanation for the effect is that we observed the natural course of IH in two patients. However, the change in clinical course after initiation of atenolol makes this unlikely. Finally, there may be currently unknown pathways through which beta-blockers mediate their effect on IH.

A randomized controlled clinical trial should be conducted to prove the equal efficacy and better tolerance of atenolol compared with propranolol.

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Chapter 4

Treatment of infantile hemangiomas with atenolol: Comparison with a historical propranolol group

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Summary

Propranolol, a lipophilic non-selective beta-blocker, has proven to be effective in the treatment of infantile hemangioma (IH). However, several side effects have been reported. Atenolol, a hydrophilic selective beta-1 blocker, could be an alternative and associated with fewer side effects.

Thirty consecutive patients with IH were treated with atenolol between June 2010 and May 2011. The therapeutic effect was judged by clinical assessment and quantified by using a Visual Analogue Scale (VAS) and the Hemangioma Activity Score (HAS). Side effects were also evaluated. The atenolol cohort was compared with a previously described cohort of 28 patients treated with propranolol between July 2008 and December 2009.

Clinical involution was present in 90% (27/30) of the IH treated with atenolol. Mild side effects occurred in 40% (12/30) of these patients and severe side effects occurred in 3% (1/30). Compared with the previously described cohort treated with propranolol, mild side effects occurred in 50% (14/28) and severe side effects in 25% (7/28) of the patients (p=0.04). Quantitative improvement of the IH in the atenolol group (n=27) showed no significant difference in either the VAS score or the HAS compared to the propranolol group (n=24).

This study indicates that atenolol is effective in the treatment of IH. Compared with a historical control group treated with propranolol, the effects of atenolol seem to be similar and less frequently associated with severe side effects. Randomized clinical trials are necessary to evaluate the efficacy and safety of atenolol treatment in IH.

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Introduction

Infantile hemangiomas (IH) are benign vascular tumors found in approximately 4-10% of Caucasian infants.[1,2] IHs can impede the function or development of neighbouring structures or organs necessitating treatment.[3]

Léauté-Labrèze et al. and others reported an impressive therapeutic response to propranolol, a lipophilic non-selective beta-blocker, in the treatment of IH.[4-15] Although the treatment of IH with propranolol has shown spectacular results, side effects, such as hypoglycemia, bronchial hyperreactivity, hyperkalemia, and diarrhoea, have been reported.[16-20)] We hypothesized that the use of a hydrophilic, selective beta-1 blocker could prevent the side effects attributable to the beta-2 activity and lipophilicity of propranolol.[20,21] The current report describes the efficacy and side effects of atenolol in 30 patients with IH. These results were compared with a previously described cohort of patients treated with propranolol.[20]

Patients and methods

Patients

Atenolol was administered as standard treatment to 30 consecutive children with IH. All IH were either potentially (life-)threatening, or had functional risk, local discomfort, or cosmetic disfigurement. This study has been received by the ethical committee of the University Medical Center Utrecht and it has not been a subject to review. The parents of the patients received written information about the effects and side effects of the treatment and they gave their consent before starting the treatment. All data was analyzed anonymously.

Patients presented at the Centre for Congenital Vascular Anomalies of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands, between June 2010 and May 2011. All patients were treated as outpatients and only admitted when indicated (e.g., age <1 months, increased risk of side effects and pain due to ulceration (requiring surgery)).

Before commencing treatment, patients were screened for contra-indications and an electrocardiogram (ECG) was performed to detect any pre-existing cardiac conduction disturbances. Patients were evaluated after approximately 2, 8 and 20 weeks. During each visit, body weight (kg), blood pressure (BP, mmHg, measured with a Dinamap), and heart rate (beats/min) were measured and digital photographs were made. During the treatment period, atenolol dosage was adjusted for weight gain. Blood glucose levels were measured only when indicated (in case of clinical signs of hypoglycemia, age <1 months, prematurity/dysmaturity and during admission). The clinician determined the clinical involution of the IH and side effects were documented and evaluated. Furthermore, parents were asked to complete a questionnaire about the efficacy and side effects of the atenolol treatment. All side effects were evaluated during the first 12 months of treatment.

The starting dosage of atenolol was 0.5 mg/kg/day (once daily). After 1 week of treatment the atenolol dosage was increased to 1 mg/kg/day. If clinical response was inadequate the atenolol dosage was gradually increased to a maximum of 3 mg/kg/day.

A previously described cohort of 28 consecutive children treated with propranolol (average dosage 2 mg/kg/day) between July 2008 and December 2009 was used as a historical control group.[20] This means that the time period, rather than the physician, defined treatment allocation to propranolol or atenolol.

The data of the atenolol group were compared with the historical propranolol group.

Efficacy assessment

Clinical assessment of efficacy.

The efficacy of atenolol (n=30) treatment was assessed by determining the clinical involution (colour change, softening to palpation and reduction in size) at the time of visit in the outpatient clinic.

The same was done in the case of patients treated with propranolol (n=28). In the case of non-cutaneous IH, additional investigations (ultrasound and/or magnetic resonance imaging (MRI)) were performed to assess efficacy.

Quantitative assessment of efficacy.

In addition to the clinical assessment, efficacy was quantified by two blinded clinical-investigators using digital photographs. These photographs were performed prior to the treatment (baseline) and after the start of treatment at 2-8 weeks (t1) and 11-24 weeks (t2). The primary 'end'point was change in the appearance of IH as evaluated on a visual analog scale (VAS). The VAS uses a 100-mm scale on which -100 represented a doubling in the size and extent of the IH, 0 represented no change/baseline and +100 represented complete disappearance.[22] The investigators were asked to mark on the VAS the changes in the size, colour and extent of the IH, comparing the photographs of t1 and t2 with baseline. To make the evaluation of efficacy more objective, the Hemangioma Activity Score (HAS)[23] was used to score the proliferative activity of the IH. Both investigators scored the photographs of baseline, t1 and t2. The change (ΔHAS) was calculated from the differences between baseline and t1 and baseline and t2. The greater the ΔHAS, the better the therapeutic effect. When both investigators assessed the IH differently (difference in VAS and/or HAS score) they came to a consensus in order to get one final score.

The non-cutaneous IH could not be scored because of lack of clinical photographs in five patients (*n*=1 for atenolol and *n*=4 for propranolol) and therefore these were excluded in the analysis of this quantitative efficacy of atenolol. Patients in the atenolol group who were previously treated with propranolol were also excluded.

Analyses

Baseline characteristics of the atenolol group and the historical propranolol group were compared with a chi-squared test. First, the percentage of patients with clinical involution of the IH was compared between the two treatment groups with a chi-squared test. Second, *t*-tests were used to calculate the difference in efficacy between the propranolol and atenolol group for both VAS and ΔHAS at t1 and t2. Third, because the photographs were not taken at exactly the same time points for all patients and some photographs of t2 were missing, a linear mixed model was used where time was modelled as a continuous variable. The model included treatment group between time and treatment. Furthermore, we adjusted for age and indication for treatment, because these variables differed between the treatment groups. The correlation between the VAS and HAS was calculated.

Results

Patients

Table 1 shows detailed characteristics of the 30 patients treated with atenolol. In all these patients the involution/improvement of the IH was clinically determined and side effects were evaluated. The median age at the time of initiation of atenolol treatment was 6.4 months (range 1.5 to 30). No significant ECG abnormalities were reported. The maximum dosage of atenolol varied between 1 – 3 mg/kg/day (average 1.2 mg/kg/day, mean 1.0 mg/kg/day). The average duration of treatment was 11.5 months (0.5-28 months). The data of the atenolol group were compared with the historical propranolol group. The detailed characteristics of the 28 patients treated with propranolol were reported earlier.[20]

To quantify the improvement of the IH, patient 4, 9, and 11 of the atenolol group were excluded because of previous treatment with propranolol (which had to be stopped due to side effects) or non-cutaneous location of the IH. The atenolol patients previously treated with propranolol were not included in the propranolol group.

Of the historical propranolol group, patients 7, 11, 18, and 19 were excluded because of non-cutaneous location of the IH. Table 2 shows the baseline characteristics of the 27 patients in the atenolol group and the 24 in the propranolol group. There was no statistically significant difference between gender distribution, location of the IH, characteristics of the IH (localised/nodular, segmental, indeterminate and multifocal) or therapeutic indication for both patient groups (all $p>0.05$). Although not significant, the atenolol group contained more patients with ulceration (30% vs 4%). The patients treated with atenolol were significantly younger compared to the patients treated with propranolol ($p=0.01$). Digital photographs at t2 were missing (because of logistical problems and/or patient no show) in three patients in the atenolol group and in three patients in the propranolol group.

Table 1. Detailed characteristics of the 30 patients treated with atenolol

Patient	Gender	Location of IH	Characteristic of IH	Indication for atenolol treatment	Previous treatment	Age at initiation of atenolol treatment (mo)	Age at end of atenolol treatment (mo)	Side effects	Maximum dosage atenolol (mg/kg)
1	F	Face (segmental IH) PHACES syndrome	segmental	functional		1.5	10		3
2	F	Buttock	localized/nodular	ulceration		5	5.5		1
3	F	Neck	indeterminate	ulceration		3	4		1
4[a]	*M*	*Groin and upper leg*	*indeterminate*	*functional*	*propranolol*	*7*	*8*	*(transient) restless sleep*	*1*
5	F	Preauricular	localized/nodular	functional		2	12		1
6	M	Chest	indeterminate	ulceration		5	12		1
7	F	Knee	indeterminate	ulceration		4	19		1
8	F	Cheek (large IH in parotid area)	localized/nodular	functional		3	[b]		2
9[a]	*F*	*Cheek*	*localized/nodular*	*functional*	*propranolol*	*26*	*54*		*1*
10	F	Face (segmental IH) PHACES syndrome	segmental	functional		3	20	constipation	2
11[a]	*M*	*Sternal intraossal IH*		*functional*		*30*	*42*	*diarrhea*	*1*
12	F	Orbita	localized/nodular	functional		7	19	(transient) restless sleep	1.5
13	F	Buttock	localized/nodular	ulceration		4.5	9		2
14	M	Lower eyelid	localized/nodular	functional		2	15	low diastolic BP	1
15	F	Chin	localized/nodular	functional		4	23	diarrhea, (transient) restless sleep	1.5

Table 1. Detailed characteristics of the 30 patients treated with atenolol *(continued)*

Patient	Gender	Location of IH	Characteristic of IH	Indication for atenolol treatment	Previous treatment	Age at initiation of atenolol treatment (mo)	Age at end of atenolol treatment (mo)	Side effects	Maximum dosage atenolol (mg/kg)
16	F	Eye and orbita	localized/nodular	functional		4	16	constipation	1
17	F	Cheek	localized/nodular	functional		1.5	15	(transient) restless sleep	2
18	F	Cheek	localized/nodular	cosmetic		4	26	(transient) restless sleep	1.5
19	F	Cheek	localized/nodular	functional		5	12	(transient) restless sleep	1
20	F	Eye	localized/nodular	functional		3	18		1.5
21	F	Lower eyelid	localized/nodular	functional		3.5	12		1
22	F	Back	localized/nodular	ulceration		4	9	(transient) restless sleep	1.5
23	M	Hand	indeterminate	functional		8	14	(transient) restless sleep	1
24	M	Ear	indeterminate	ulceration		2	15		1.6
25	F	Scalp	localized/nodular	ulceration		6	19		1
26	M	Forehead, scrotum, thorax	localized/nodular	cosmetic		8	17		1
27	F	Lower lip (back)	localized/nodular	functional		5	16		1
28	M	Upper eyelid	localized/nodular	functional		2	17		2
29	M	Forehead	localized/nodular	cosmetic		7	26		1.5
30	F	Hand, upper leg	indeterminate	functional		1.5	17		1

PHACES syndrome (**P**osterior fossa abnormalities, **H**emangiomas, **A**rterial abnormalities, **C**ardiac anomalies, **E**ye anomalies, **S**ternal agenesia or **S**upra-umbilical raphe).

[a] To quantify the improvement of the infantile haemangiomas (IH) patient 4, 9, and 11 were excluded because of previous treatment with propranolol or non-cutaneous location of the IH.

[b] still on atenolol treatment.

Table 2. Baseline characteristics of the patients in the atenolol and the historical propranolol group.

		Atenolol n=27	(%)	Propranolol =24 [a]	(%)	p-value
Gender	Male	7	26	6	25	0.94
	Female	20	74	18	75	
Location IH	Face and neck	21	78	22	92	0.17
	Other parts of the body (except face)	6	22	2	8	
Characteristic IH	Localized/nodular	19	70	19	79	0.36
	Segmental	2	8	3	13	
	Indeterminate	6	22	2	8	
	Multifocal (5 or more IH)	0	0	0	0	
Indication of treatment	Functional	16	59	20	83	0.07
	Ulceration	8	30	1	4	
	Cosmetic	3	11	2	8	
	Diagnostic	0	0	1	4	
Age at initiation of treatment	1-6 months	23	85	12	50	0.01
	6-12 months	4	15	8	33	
	>12 months	0	0	4	17	

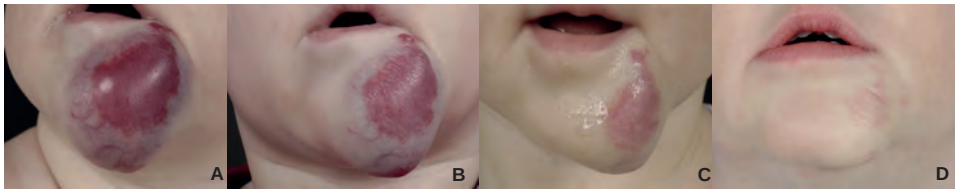
For the quantified assessment of the improvement of the infantile hemangiomas (IH) patients with non-cutaneous IH and patients in the atenolol group who were previously treated with propranolol were excluded.

[a] Historical propranolol group.[20]

Efficacy of atenolol

In the atenolol group 27 out of 30 patients (90%) showed clinical involution at t1, at 2-8 weeks after start of treatment. Figure 1a and 1b show examples of two patients treated with atenolol.

a



b

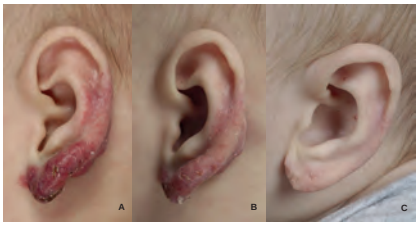


Fig 1 (a). Patient 15. **A**, baseline (before treatment). **B**, t1: 5 weeks after start of atenolol treatment (age 5 months). **C**, t2: 19 weeks after start of atenolol treatment (age 8.5 months). **D**, 16 months after start of atenolol treatment (age 20 months). Photograph D was not included in the study.
(b). Patient 24. **A**, baseline (before treatment). **B**, t1: 4 weeks after start of atenolol treatment (age 3 months). **C**, t2: 20 weeks after start of atenolol treatment (age 7 months).

Clinical assessment of efficacy compared with propranolol (atenolol n=30, propranolol n=28).

Two patients (patients 2 and 3) with an ulcerated IH showed insufficient response after two weeks of atenolol treatment (1 mg/kg/day), with respect to ulceration and pain, and the ulcer was excision. Patient 3 did not respond to treatment with propranolol 2 mg/kg/day as well. Patient 1, with a segmental IH in the face affecting her right eye, initially responded well on atenolol treatment. However, the effect on the IH of the upper eyelid of the right eye was insufficient and surgical debulking was inevitable.

In the historical propranolol group all patients (100%) showed clinical involution (color change, softening to palpation and reduction in size) at t1 (p=0.09).

Quantitative assessment of efficacy of atenolol (n=27) compared with the historical propranolol group (n=24).

The scores of both VAS and HAS for the quantitative improvement of the IH are shown in Figure 2(a and b). Figure 2(a) shows the VAS scores of both treatment groups and Figure 2(b) shows the difference in scores between baseline and t1 and between baseline and t2 (ΔHAS) for both treatment groups. Both scores at t1 were slightly higher in the propranolol group and at t2 the VAS score was almost equal in both groups and the ΔHAS was slightly higher in the atenolol group. However, these differences were statistically not significant (all $p>0.05$). The average time of the first photograph taken for atenolol was 3.0 weeks (range 2-6) and for the second photograph 14.9 weeks (range 11-20). For propranolol the average time of the photographs was respectively 3.9 weeks (range 2-8) and 14.9 weeks (range 11-24).

The interaction between treatment and time was not significant in the linear mixed model for both scores (VAS $p=0.44$ and HAS $p=0.32$), which means that the trend over time with respect to the scores of the IH did not differ between the treatment groups. Before adjustment for baseline characteristics the VAS score was slightly higher in the propranolol group but statistically not significant ($p=0.44$). The ΔHAS was the same in both groups ($p=0.88$). After adjustment for age and indication for treatment, the VAS score was higher in the historical propranolol group and the ΔHAS was higher in the atenolol group. Both differences were statistically not significant (respectively $p=0.34$ and $p=0.39$).

The VAS and HAS showed a good correlation at t1 and t2 of respectively 0.58 and 0.59 ($p<0.001$).

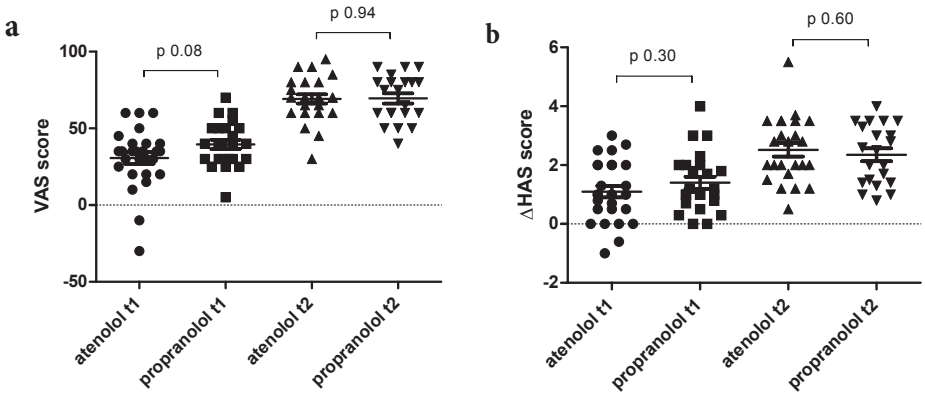


Fig 2 (a). VAS scores of the efficacy of atenolol and propranolol. The efficacy of atenolol and propranolol was scored on a Visual Analogue Scale (VAS) at t1 and t2. P-values show no significant ($p < 0.05$) difference between both drugs.

(b). ΔHAS scores of the efficacy of atenolol and propranolol. The efficacy of atenolol and propranolol was scored with the Haemangioma Activity Score (HAS) at t1 and t2 and ΔHAS (difference between baseline and t1 and baseline and t2) was calculated. P-values show no significant ($p < 0.05$) difference between both drugs.

Side effects of atenolol

All atenolol patients (*n*=30) showed a decrease in BP. Only patient 14 once showed a diastolic BP below the 5th percentile for age (BP 66/29, 5th percentile (p5) for diastolic pressure at age 2 months = 33 mmHg) during treatment (pre-treatment BP 84/51 (50th percentile)). Serious signs suggestive of organ hypoperfusion (such as loss of consciousness) were not observed and finally the dosage of atenolol was increased in this patient without showing a low BP. All other patients showed BP above the p5 for age and were asymptomatic, although some of the parents reported cold extremities. Eight patients suffered from (transient) restless sleep (patient 4, 12, 15, 17, 18, 19, 22, and 23). Patient 4 was previously treated with propranolol, which was stopped because of bronchial hyperreactivity and restless sleep. During atenolol treatment the patient again suffered from restless sleep. After cessation of atenolol treatment, the patient regained a normal sleeping pattern. The other patients suffered from mild and transient restless sleep.

Other side effects reported by parents were constipation in two patients (7%) and diarrhoea in two other (7%). Infection as a cause of diarrhea was not excluded.

None of the patients suffered from hypoglycemia or bronchial hyperreactivity.

The side effects of atenolol (*n*=30) were compared with the side effects of the historical propranolol group (*n*=28).[20] Table 3 summarizes the side effects in both treatment groups. Severe side effects (hypoglycemia, bronchial hyperreactivity and hypotension) occurred in 3% (1/30) of patients treated with atenolol and in 25% (7/28) treated with propranolol (p=0.04). Mild side effects (restless sleep, constipation and diarrhea) occurred in 40% (12/30) of patients treated with atenolol and in 50% (14/28) of patients treated with propranolol (p=0.44).

Table 3. Side effects in patients treated with atenolol compared with the historical propranolol group.

	Atenolol n=30 (%)	**Propranolol n=28 (%)[a]**
Severe side effects		
Hypoglycemia	-	2 (7)
Bronchial hyperreactivity	-	4 (14)
Hypotension	1 (3)	1 (4)
Mild side effects		
Restless sleep	8 (27)	11 (39)
Constipation	2 (7)	3 (11)
Diarrhoea	2 (7)	-

Some patients had multiple side effects.

Hypotension means a diastolic blood pressure below the 5th percentile for age.

[a] Historical propranolol group.[20]

Discussion

Since the report of Léauté-Labrèze et al., the treatment of IH with beta-blockers has become the treatment of choice.[4,24,25] As far as we know, only one randomized controlled trial (RCT) has proven the effectiveness of propranolol.[(26)] Nevertheless, there seems to be a general agreement that propranolol is effective in IH treatment and studies now focus on optimal treatment regimen and on beta-blockers with a more favorable balance between efficacy and side effects.[21,25,27-30] The results of this study confirm that atenolol is effective in the treatment of IH. Moreover, when compared to a historical control group, atenolol seems to be as effective as propranolol but appears associated with fewer side effects.

Atenolol is a hydrophilic, selective beta-1 blocker and therefore is not associated with side effects attributable to beta-2 activity and lipophilicity observed with propranolol. It has a terminal half-life of 6-8 hours and therefore has to be administered only once daily, which may improve patient compliance.[31,32]

Itinteang et al.[33] suggested that propranolol acts via the renin-angiotensin system in regulating accelerated involution of proliferating IH by decreasing renin production in the kidneys. As the kidneys predominantly express beta-1 receptors, the renin-angiotensin-aldosterone system (RAAS) is most likely the missing link in understanding the working mechanism of both beta-blockers and angiotensin-converting enzyme (ACE) inhibitors in the treatment of IH.[30] Another explanation, for the effect of atenolol in the treatment of IH, besides currently unknown mechanisms, could be the limited beta-2 blocking potential of atenolol.[34]

Atenolol treatment was clinically effective in 27 patients (90%). Two patients (patient 2 and 3) did not respond after two weeks of treatment with atenolol with respect to pain and ulceration. Besides a low starting dose it is possible that atenolol treatment was started too late and/or discontinued too early. Quantitative comparison of the efficacy of atenolol and propranolol using a historical study group showed no significant difference (all $p>0.05$).

Although rare, symptomatic hypoglycemia can be a serious complication of propranolol treatment. In our previous described cohort treated with propranolol, two patients with hypoglycemia were reported, of which one with adrenocortical suppression due to steroid withdrawal, and three patients who had to discontinue propranolol treatment due to bronchial hyperreactivity.[20] In the group of patients treated with atenolol, no hypoglycemia or bronchial hyperreactivity was observed and even a patient in whom propranolol had to be discontinued due to bronchial hyperreactivity responded well to atenolol treatment. This confirms our hypothesis that the use of a hydrophilic beta-1 antagonist reduces beta-2 receptor blockade and subsequently decreases the risk of hypoglycemia and pulmonary side effects.[35-38] Atenolol is theoretically less likely to produce central nervous system (CNS)-related side effects, such as nightmares and hallucinations, compared to lipophilic

beta-blockers.[39,40] However, studies in children are lacking. Eight of the patients treated with atenolol suffered from restless sleep, suggesting that most probably atenolol (despite its hydrophilicity) can cross the blood-brain barrier in high-enough concentrations to induce CNS-related side effects.[39] In most of the patients the restless sleep was very mild and transient.

This is the first study comparing two different beta-blockers. The patients in the atenolol group were new consecutive patients treated with atenolol. These patients were compared to a historical control group (consecutive patients treated with propranolol). The decision to treat the patients with either propranolol or atenolol was only based on the period in time and not on patient characteristics, which reduces the chance of confounding. Differences that might have influenced the results between the atenolol and propranolol group were that the former were younger, were less frequently seen, and were treated once/day instead of twice. On the one hand, because of the young age of the patients in the atenolol group, the chance that the effect was not due to the treatment but to the natural involution of the IH is unlikely. On the other hand a younger age may be associated with a better response to treatment. Therefore we corrected for age in the linear mixed model. The efficacy in both patient groups was quantified by the same blinded investigators, differences in baseline characteristics were adjusted in the statistical analyses, and the improvement of the IH was scored as objective as possible.

Propranolol and atenolol have been used extensively by pediatric cardiologists for many years. However, there are still many unanswered questions for their usage in treating IH. Hard data is lacking about the preferred age to initiate treatment of IH, the optimal dosage, the duration of treatment, and the criteria for discontinuing treatment.

It is unknown whether the long-term outcome of the treatment with beta-blockers for cosmetic indications is favorable above the natural course. Data are also lacking about the possible side effects of long-term treatment of healthy children with beta-blockers. However, propranolol seems to reduce subsequent memory for both new and previously learned emotional material in healthy adults.[41] More prospective long-term clinical studies about the response rate and side effects in the treatment of IH with beta-blockers are necessary.

Conclusion

This study shows that atenolol is effective in the treatment of IH. Compared with a historical cohort of patients treated with propranolol, atenolol seems to have a similar effect on IH. Furthermore atenolol seems to be less frequently associated with potentially (life-) threatening side effects. Further clinical studies are necessary to confirm the described effects and safety of atenolol.

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Part I I

The pediatric perspective on IH treatment guidelines

Chapter 5

Is cardiovascular evaluation necessary prior to and during beta-blocker therapy for infantile hemangiomas?

A cohort study

Martine F Raphael, Corstiaan C Breugem, Florine AE Vlasveld, Marlies de Graaf, Martijn G Slieker, Suzanne GMA Pasmans, Johannes MPJ Breur

Abstract

Background Although consensus guidelines for pretreatment evaluation and monitoring of propranolol therapy in patients with infantile hemangiomas (IH) have been formulated, little is known about the cardiovascular side effects.

Objectives We sought to analyze cardiovascular evaluations in IH patients at baseline and during treatment with an oral beta-blocker.

Methods Data from 109 IH patients were retrospectively analyzed. Patient and family history, pretreatment electrocardiogram (ECG), heart rate and blood pressure were evaluated before initiation of beta-blocker therapy. Blood pressure and standardized questionnaires addressing side effects were evaluated during treatment.

Results Questionnaire analyses (n=83) identified 3 cases with a family history of cardiovascular disease in first-degree relatives. ECG findings were normal in each case and no serious complications of therapy occurred. ECG abnormalities were found in 6.5% of patients but there were no contraindications to beta-blocker therapy and no major complications. Hypotension in 9 patients did not require therapy adjustment. In all, 88 parents (81%) reported side effects during beta-blocker treatment.

Limitations The relatively small patient cohort is a limitation.

Conclusion Pretreatment ECG is of limited value for patients with an unremarkable cardiovascular history and a normal heart rate and blood pressure. Hypotension may occur during treatment.

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Introduction

Infantile hemangiomas (IH) are common with a 9.9% prevalence in the Dutch population. (1) In 2008, Léauté-Labrèze et al. reported a remarkable response to treatment with the non-selective beta-blocker propranolol (2). As we encountered adverse effects such as hypoglycemia and bronchial hyperreactivity in several patients with IH treated with propranolol, (3) atenolol (a hydrophilic selective beta-1-receptor blocker) has become our primary treatment choice. (4,5)

Consensus guidelines for pretreatment evaluation and monitoring of propranolol therapy in infants with IH were formulated recently. (6) These include a pretreatment electrocardiogram (ECG) if the heart rate (HR) is below normal, if arrhythmia is detected on cardiac examination, or if there is a family history of arrhythmias or maternal connective tissue disease. Repeated cardiovascular monitoring is not advocated, unless the dose of propranolol is altered in patients without comorbidity showing normal vital signs during the first hours after therapy initiation; this corresponds with the peak effect of oral propranolol on HR and blood pressure (BP) 1 to 3 hours after administration.

Despite these recommendations, the value and necessity of pretreatment screening examinations and monitoring remain unclear. This prompted us to acquire cardiovascular data from all our patients with IH treated with beta-blockers (Fig 1) with the aim of providing evidence-based data for future treatment recommendations.

Methods

Patients

All consecutive patients treated with propranolol or atenolol for IH at the Center for Congenital Vascular Anomalies (CAVU) of the Children's Hospital Utrecht, between July 2008 and August 2012, were included in the study. Parents received written information about the possible effects and side effects of oral beta-blockers and gave their consent before starting treatment. All data were retrospectively and anonymously analyzed from questionnaires and medical records. Approval by the institutional ethics committee was obtained (protocol nr 12-501).

Patients were treated as outpatients and only hospitalized when indicated (e.g. age < 1 month, increased risk of side effects, or pain caused by ulceration; see protocol) (Fig 1). The indication for initiation of therapy was noted. The starting dose of propranolol was 1 mg/kg/day (in 2 divided doses) and was increased to 2 mg/kg/day after at least 5 doses. During treatment, the dose was adjusted for weight gain. If the clinical response was inadequate, the dose of propranolol was increased stepwise to a maximum of 4 mg/kg/day. The starting dose of atenolol was 0.5 mg/kg/day (once daily). After one week of treatment, the dose was

increased to 1 mg/kg/day and adjusted for weight during treatment. If clinical response was inadequate, the dose of atenolol was gradually increased to a maximum of 3 mg/kg/day.

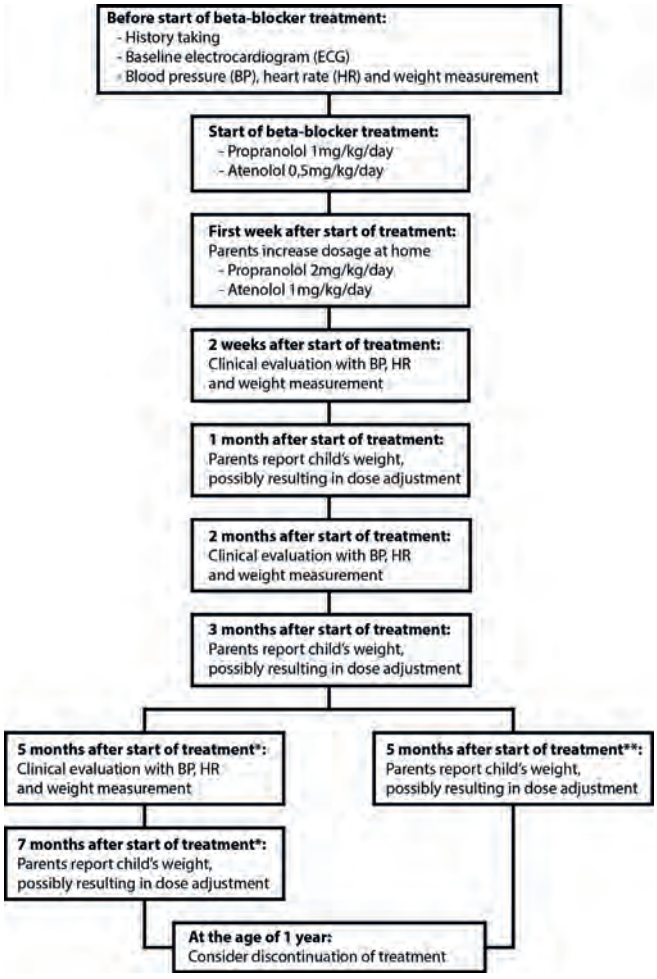

Fig. 1: Flowchart pretreatment evaluation and monitoring protocol of beta-blocker treatment
* Patients younger than 6 months of age at initiation of beta-blocker therapy had an extra follow-up visit at 5 months of age
** Children older than 6 months of age at initiation

Patient history

Patients were screened for contra-indications to treatment during their first outpatient visit. Parents were asked about their child's development, existence of co-morbidities, and family history of cardiovascular disease. We conducted an extensive parental survey for each

patient emphasizing potential risks for beta-blocker use (available as online supplement). The questionnaire inquired whether the patient had a heart condition or if the child had ever experienced loss of consciousness. A history of relatives with congenital heart disease, cardiac arrhythmias, heart disease before the age of 60 years or death from unknown cause before the age of 40 years, was also documented.

Electrocardiogram

A pre-treatment ECG was performed and examined by a pediatric cardiologist to detect bradycardia and/or any pre-existing cardiac conduction disturbance. Bradycardia was defined as HR below normal for gender and age. (7) If abnormalities were detected, the infant was clinically evaluated by a pediatric cardiologist, including cardiac ultrasound (CU) if indicated, to ensure that beta-blocker therapy could be safely initiated.

Blood pressure

Blood pressure measurements were carried out by experienced hospital staff members using a Dinamap (GE Healthcare, Waukesha, USA) with an age-sized cuff. BP was monitored at baseline and at 2 weeks, 2 months and 5 months (for infants younger than 6 months at onset of treatment) after initiation of propranolol or atenolol therapy (Fig 1). Afterwards measurements were performed as required on an individual basis. Systolic and diastolic BP measurements were converted into age and gender corrected Z-scores by using the percentiles of the normal BP for children. (8) Hypotension was defined as a systolic or diastolic BP below the 5th percentile, corresponding to a Z-score of < -1.64. (8)

Side effects

The electronic medical records (EMR) were screened for possible side effects of beta-blocker therapy during follow-up examination. After we introduced atenolol as a therapeutic agent, parents were asked to fill out standardized questionnaires on side effects at every outpatient visit. This gave us insight into the occurrence of side effects from both physicians and parents. Serious complications were defined as (asymptomatic) hypotension, pulmonary symptoms related to direct blockade of adrenergic bronchodilatation, hypoglycemia, syncope or (hypoglycemic) seizures.

Statistical methods

Differences between patients taking atenolol or propranolol were analyzed using unpaired Student t-test for normally distributed continuous variables and Chi-square test for discrete variables. Differences in BP before and after initiation of medication were analyzed using paired Student t-test. All tests were performed using SPSS 20.0 (IBM Corp, Armonk, NY).

Results

Patients

A total of 110 patients were prescribed beta-blocker therapy for IH during the study period. Data from 109 patients were available for statistical analysis. One patient was lost to follow-up shortly after starting treatment. Median age at initiation of treatment was 4.0 months (range 0-48 months); 3 patients were under 1 month of age. There were 81 female and 28 male patients. Further baseline patient characteristics can be found in Table 1.

Table 1: Baseline patient characteristics (n = 109)

Characteristics	Propranolol (n=45)*	Atenolol (n=64)**	Total (n = 109)	P-Value
Gender:				
Female (%)	35 (78%)	46 (72%)	81 (74%)	0.49
Male (%)	10 (22%)	18 (28%)	28 (26%)	
Age at start of treatment:				
Median age in months (range)	5 (0-43)	4 (0-48)	4 (0-48)	0.04
Age < 1 month	2 (4%)	1 (2%)	3 (3%)	0.57 #
PHACES	1 (2%)	1 (2%)	2 (2%)	1.0 #
LUMBAR	1 (2%)	0	1 (1%)	0.41 #
Treatment indication				
(Risk of) Functional impairment	39 (87%)	40 (63%)	79 (72%)	0.005
Local discomfort due to ulceration	4 (9%)	13 (20%)	17 (16%)	0.11
Cosmetic disfigurement	3 (7%)	15 (23%)	18 (17%)	0.02
Localization of hemangioma* **				
Head	38 (84%)	46 (72%)	77 (71%)	0.12
Extremities	8 (18%)	15 (23%)	23 (21%)	0.48
Buttock	1 (2%)	4 (6%)	5 (5%)	0.40 #
Genitalia	2 (4%)	3 (5%)	5 (5%)	1.0 #
Trunk	10 (22%)	6 (9%)	16 (15%)	0.06
Neck	1 (2%)	2 (3%)	3 (3%)	1.0 #
Liver	1 (2%)	0	1 (1%)	0.41 #

LUMBAR = Lower body infantile hemangioma and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformities, Anorectal malformations and Arterial anomalies and Renal anomalies; PHACES = Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects and/or coarctation of the Aorta, Eye abnormalities and Sternal abnormalities or ventral developmental defects.

* Five patients switched from propranolol to atenolol therapy.

** Two patients switched from atenolol to propranolol therapy.

*** Several patients had multiple infantile hemangiomas.

#Fisher's exact test

Patient history

Surveys were mailed to 108 parents of which 84 (78%) were completed. One family emigrated during the initiation of the survey. Because parental permission to use the data for research purposes was not obtained in 1 case, 83 surveys (77%) were eventually included in the data analysis. According to this parental survey, 3 children had a family history of cardiovascular disease or arrhythmias in first-degree relatives (maternal atrioventricular (AV) septal defect (AVSD), maternal first degree AV block and paternal angina pectoris). These children showed no ECG abnormalities and experienced no serious complications from beta-blocker treatment. Four patients (5%) had existing co-morbidities consisting of cow milk allergy, eczema and a physiologic cardiac murmur (n=1); a physiologic cardiac murmur (n=1); a small ventricular septal defect, which closed spontaneously shortly after birth (n=1); and coarctation of the aortic arch for which cardiac surgery was performed (n=1) (Fig 2).

Electrocardiogram

A baseline ECG was performed In 107 of 109 patients. The remaining 2 were the first patients treated with beta-blockers at our institution and treatment was initiated during an uncomplicated 3-day admission period with continuous bedside ECG monitoring. Seven of 107 (6.5%) patients showed ECG abnormalities, for which pediatric cardiac consultation was obtained (Fig 2). Abnormalities were: postoperative right bundle branch block (RBBB) (n=1), early repolarization (n=1), atrial rhythm and non-specific intraventricular conduction delay (n=1), non-specific intraventricular conduction delay (n=3) and borderline prolonged QTc interval (n=1). In 1 patient with a borderline prolonged QTc interval a CU was not performed. Cardiac ultrasound findings and the concluding report from the cardiologist did not identify a contra-indication to beta-blocker therapy in these 7 patients. No major complications occurred during treatment. In 108 patients, the baseline HR corrected for age and sex revealed no evidence of bradycardia. One child underwent pretreatment consultation in another institution and HR measurement was not reported in our EMR.

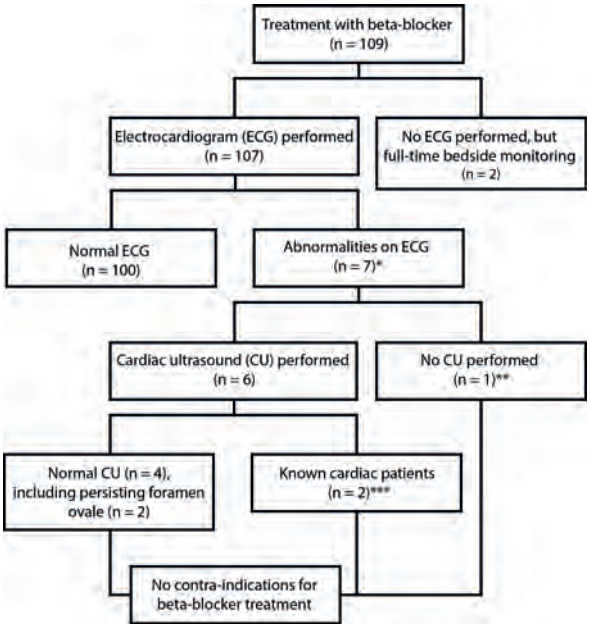

Fig. 2: Flowchart outcome pretreatment electrocardiogram (ECG)
* ECG findings: postoperative right bundle branch block (RBBB) (n=1), early repolarization (n=1), atrial rhythm and non-specific intraventricular conduction delay (n=1), non-specific intraventricular conduction delay (n=3), borderline prolonged QTc interval (n=1)
** This patients' ECG revealed a borderline prolonged QTc interval for which no further investigation was performed.
*** 1 patient underwent surgical intervention for atrial and ventricular septal defect. Another patient suffered from an interrupted aortic arch type C with secondary atresia of the left carotid artery by PHACES, for which cardiac surgery was performed. (PHACES = Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects and/or coarctation of the Aorta, Eye abnormalities and Sternal abnormalities or ventral developmental defects)

Blood pressure

In patients treated with propranolol, systolic BP did not decrease significantly after initiation of therapy (Fig 3a). There was a significant decrease in diastolic BP (mean 0.59 [CI 0.01 - 1.17]) in the first two weeks of therapy. In the atenolol group, both systolic and diastolic BP decreased significantly after initiation of treatment (mean 0.96 [CI 0.44 -1.48] and mean 0.42 [CI 0.03 – 0.82], respectively) (Fig 3b). When comparing beta-blockers, no significant difference in decrease in either systolic or diastolic BP was found. During treatment, 9 patients were found to have hypotension (diastolic BP below the fifth percentile (n =5) or systolic BP below the fifth percentile (n = 4)). Because these patients with reported low systolic or diastolic blood pressure showed no serious complications at the time of measurement or afterwards, beta-blocker therapy was continued in all.

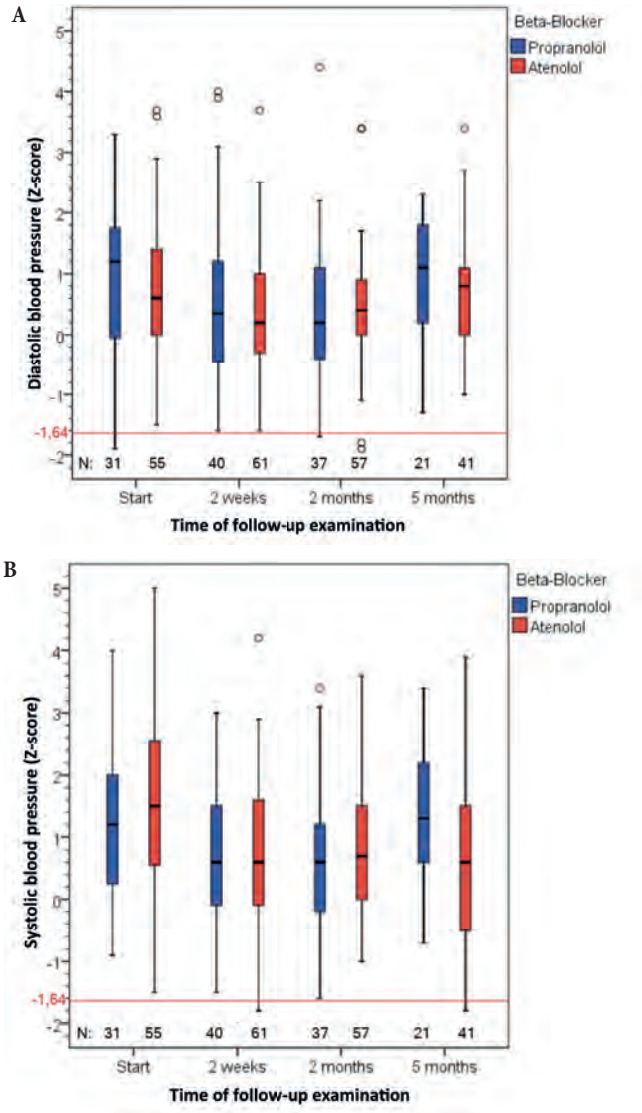

Fig. 3: Blood pressure measurements during beta-blocker treatment
Diastolic (A) and systolic (B) BP values from patients on propranolol or atenolol therapy
N = number of patients
Start = before initiation of beta-blocker therapy, 2 weeks = 2 weeks after initiation, 2 months = 2 months after start, 5 months = 5 months after start (only in children younger than 6 months at initiation of beta-blocker therapy)
Line -1.64 = Z- score under which aboslute hypotension is defined
In all the box plots, the top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the line of the middle represents the 50th percentile. Open circles represent outliers of the BP Z-score.

Side effects

In total, the parents of 88/109 children (81%) reported side effects during treatment (Table 2). In 6% of patients dyspnea / shortness of breath was noted. Other serious or potentially life-threatening side effects such as syncope (2%), seizure (1%) and suspected hypoglycemia (3%) are specified in Table 3. Proven hypoglycemia occurred in 1 patient (1%) during propranolol treatment. (9)

Table 2 Reported side effects

Side effects	**Patients on beta-blocker (n =109)**
Very frequently reported (>10%)	
Cold extremities	55 (51%)
Sleep disturbance	47 (43%)
Gastro-intestinal problems	27 (25%)
Fatigue	20 (18%)
Coughing	19 (17%)
Sweating	16 (15%)
Pallor	14 (13%)
Agitation/irritation	14 (13%)
Frequently reported (1-10%)	
Dyspnea/shortness of breath	6 (6%)
Increased activity	5 (5%)
Skin reaction*	5 (5%)
Nausea/Vomiting	4 (4%)
Decreased appetite	4 (4%)
Increased appetite	3 (3%)
Hypoglycemia**	3 (3%)
Syncope	2 (2%)
Dizziness	2 (2%)
Hair loss	2 (2%)
Incidentally reported (0,1-1%)	
Seizure	1 (1%)
Dry mouth (xerostomia)	1 (1%)
Hallucinations	1 (1%)
Headache	1 (1%)
TOTAL***	88 (81%)

* Dry skin (n=3), eczema (n=1), rash (n=1)

** One child with proven hypoglycemia and 2 children with symptoms of possible hypoglycemia.

***Some children reported more than one side effect.

Table 3 Serious or potentially life-threatening adverse events

Case	Beta-blocker	Symptoms	Possible cause	Results
1-year-old girl on tapering dose of systemic steroid therapy	Propranolol	Multiple episodes of decreased level of consciousness	Proven hypoglycemia secondary to beta-blocker use and adrenal insufficiency on withdrawal of steroid therapy	Hospital admission for intravenous glucose
3-year-old girl	Propranolol	Nausea but desired food	Suspected hypoglycemia	Recovered quickly after eating
2-month-old girl	Propranolol	Epileptic seizure 5 hours after first dose of beta-blocker	Unknown	Restarted propranolol without complications
5- month-old girl	Atenolol	Difficulty waking and hypotonic after a period of fasting	Suspected hypoglycemia	Recovered quickly after eating
2- year-old girl	Atenolol	Two episodes of loss of consciousness, one after increase in dosage	Syncope of unknown origin	Atenolol was restarted without complications
11-month-old girl	Atenolol	Three episodes of loss of consciousness	Syncope of unknown origin	Treatment was continued

Discussion

This study of cardiovascular results obtained while following a pretreatment and monitoring protocol for patients with IH receiving beta-blocker therapy supports the recently published guidelines. (6) It adds useful information for future guidelines and hopefully will provide an impetus for further research. We acknowledge that it is hard to draw definite conclusions from our relatively small patient cohort. Because the objective of our study was not to differentiate between adverse effects of propranolol and atenolol, it is not possible to compare medication safety profiles.

Although 7% of infants showed ECG abnormalities for which a pediatric cardiologist was consulted, no patient had sick sinus syndrome (SSS), atrioventricular block (AVB) or bradycardia. Since the incidence of SSS and AVB is low, the number of ECGs necessary to diagnose a single case is at least 20,000. (10) The questionnaire revealed a family history of cardiovascular disease in 4% of the infants. These patients had normal ECGs and showed no complications during beta-blocker treatment. If ECGs were reserved only for infants at risk, ie, those with bradycardia and/or a positive (family) history at initiation, the number of ECGs would be reduced by 95%. This would have resulted in fewer referrals to a pediatric cardiologist, altogether resulting in a significant cost reduction. We conclude that in cases with an unremarkable patient and family history and a normal HR, ECGs are probably of no additional pretreatment value.

To discern patients potentially at risk, an accurate cardiovascular medical history and a thorough physical examination at first consultation are vital for identifying contra-indications to treatment, as stated in the consensus guidelines. The medical history should include questions about syncope or near-syncope, shortness of breath, diaphoresis and wheezing. (6,11) Key questions from the family history are the occurrence of heart block, arrhythmia, sudden death, congenital heart disease, maternal connective tissue disease or syncope. (6,11) Physical examination should include HR and rhythm, BP and cardiac and pulmonary assessment. (6,11)

The consensus guidelines recommend HR and BP measurements 1 and 2 hours after initiation of beta-blocker therapy and after a significant dose increase. (6) Routine cardiovascular monitoring is not recommended after at least 1 set of normal measurements once the target dose has been achieved. Although the effect of beta blockers on BP can be seen shortly after the first dose, Fagan et al. showed that the maximal effect is reached after 48 hours, corresponding with the accumulation of propranolol to steady state in plasma. (12) Our data show that both asymptomatic hypotension and a significant decrease in systolic and diastolic BP during follow-up can be missed, by following the recommendations of the consensus protocol. Although hypotension we observed was considered not clinically relevant and had no therapeutic consequences, it is important to be aware that it occurs in this healthy pediatric population. BP measurements at fixed time-points during follow-up

are probably not necessary but evaluation should questions about symptoms, providing data for therapy adjustment.

The vast majority of frequently reported side effects are transient and mild. It is imperative for caregivers and professionals to be educated to recognize possible side effects of beta-blocker treatment in patients with IH and act accordingly. This information should be given to the family at first consultation.

In conclusion, this study demonstrates that in the setting of an unremarkable patient and family history and a normal HR and BP at initiation of beta-blocker treatment, ECG is probably of no additional value as a pretreatment screening tool. Our data illustrate that dose response effects of beta-blocker therapy on BP are seen during follow-up. Although asymptomatic hypotension was not a reason to adjust therapy in this cohort, we are unsure about what influence this adverse effect has on cardiovascular, gross motor or neurocognitive systems in the long term. A limitation of the study was the relatively small sample size.

Acknowledgements

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Chapter 6

Treatment of infantile hemangiomas: therapeutic options in regard to side effects and adverse events – a review of literature

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Abstract

Introduction While options for treatment strategies for infantile hemangiomas (IH) are numerous, evidence-based information about agents, optimal dosage, adverse effects, treatment modality, pretreatment and treatment strategies remain limited.

Areas covered To evaluate side effects and adverse events of medical treatment in children with infantile hemangioma, a comprehensive review of literature was performed to provide information for daily practice. In total 254 studies were retrieved from medical databases and comprised 10.022 patients divided in 5 different treatment groups. Information about working mechanism, side effects and adverse events of therapies used as a single agent for IH are discussed and evaluated according to information from pharmacotherapeutic databases. Randomized controlled trials have only scarcely been performed for the many therapeutic options reported for IH. Short- and long-term side effects and adverse events, have not been systematically studied. Subsequently information about the medical treatment options and pharmacotheraputic databases for therapy in children with IH are incomplete.

Expert opinion From the many therapeutic options, propranolol is the first-line approach for IH, predominantly based on clinical observation, efficacy and tolerability in the short-term. The unsolved ravels of possible short- and long-term adverse events of propranolol used during early developmental stages of children need thorough review.

Expert Opinion on Drug and Safety. 2016 Feb;15(2):199-214.

Introduction

Infantile hemangiomas (IH) are the most frequently observed vascular tumors in infancy, found in 4-10% of Caucasian infants [1,2]. Several therapeutic regimens have been used to treat these benign tumors, with various outcomes. While options for treatment strategies for IH are numerous, evidence-based information about agents, optimal dosage, treatment modality, pretreatment and treatment strategies remain limited. In addition, side effects and adverse effects from treatment of IH are rarely systematically reported. The study of Léauté-Labrèze et al published in 2008, demonstrated remarkable treatment results with the non-selective beta-blocker propranolol on IH [3]. Consensus guidelines for pretreatment evaluation and monitoring of propranolol therapy for IH were proposed [4]. Side effects and adverse events reported in this guideline are bradycardia, hypotension, hypoglycaemia, broncohspasm and hyperkalemia. In routine clinical practice, propranolol appears to be effective for IH, well tolerated, and better than previous therapies at inducing regression. These observations, in conjunction with the immediate availability of the medication in pediatric formulations, resulted in the rapid and widespread adoption of propranolol for treatment of IH. This apparent success may also lead to a shift in treatment indications from initially functional only to cosmetic indications. Considering the potential overuse of beta-blockers for uncomplicated IH and the uncertainty about short- but especially long-term potential side effects and adverse events prompted us to review literature about what is already known.

We aimed to conduct a literature review of all medical therapeutic options for IH in children to provide a more safe and optimal case-based, treatment approach, as well as monitoring. We specifically studied treatment mechanism of action, side effects and adverse events. General information about side effects and adverse effects of these treatment strategies from pharmacotherapeutic databases was added. Our aim was to make treatment recommendations and follow-up protocols for daily practice and subsequently highlight gaps that currently exist and which should be addressed in future clinical studies.

Methods

Data source and search strategy

MEDLINE, EMBASE and Cochrane Library were searched in April 2014 for the search terms *(treatment OR therapy) AND (hemangioma OR hemangiomas) AND (children OR infantile OR child OR juvenile OR adolescent OR neonate OR newborn OR infant)* and applied data limitation, starting from January 2008 until May 2014. The reference management program RefWorks was used for the saving and de-duplication of the articles.

Selection criteria:

We included studies describing medical treatment for children aged ≤18 years with IH. The selected studies had to clearly describe whether side effects or adverse events had occurred, either with detailed symptoms or no occurrence. Studies were excluded if they focused on either surgical or laser treatment or photo- or radiotherapy. Studies not written in English, Dutch, French or German were excluded, as were reviews and meta-analyses.

Study selection:

Three independent researchers (F.V. & N.E. & M.R.) conducted the systematic search. The selection process was performed as follows:

1. Screen resulting articles for double publications
2. Screen all hits on article type and language (exclude articles meeting exclusion criteria for article type or language)
3. Screen all abstracts on relevance (exclude articles beyond the scope of this research)
4. Screen full text on relevance if available (include articles reporting medical treatment for children ≤18 years of age with an IH and reporting side effects and adverse events) and if full text was not available, but all necessary information (i.e. number of patients, medicine, dose, side effects and adverse events) was listed in the abstract, the particular publication was included as well
5. Article citation screening (add articles which met the inclusion criteria)

The researchers compared the articles remaining after this selection process, and discrepancies between reviewers were resolved by consensus.

Data extraction

Two reviewers (F.V. and M.R.) listed all included manuscripts. Number of patients, type of medication, dosage, side effects and reported adverse events were registered in a database. If more than one treatment medication was used in a study, data were selected from the different treatment groups and listed as separate substudies regarding therapy and adverse effects from the included study. Available literature was evaluated for its hierarchy level of evidence (I – V)[5].

Data analysis

The pediatric hospital pharmacist (Y.L.) analyzed reported side effects and adverse events of the medications mentioned in the included articles by using national and international pharmacotherapeutic adult databases. [6-10] The pharmacist added possible serious side effects and adverse events of used medications that were not reported in the systematic literature search.

Results

Search results

Initially 1969 potential eligible studies were identified in the literature search. After excluding double reports 1287 unique articles remained. A total of 254 studies met all inclusion criteria for this review (Figure 1 Flowchart according the four-phase flow diagram of PRISMA [11]). No third party arbitration was needed for the discrepancies between reviewers.

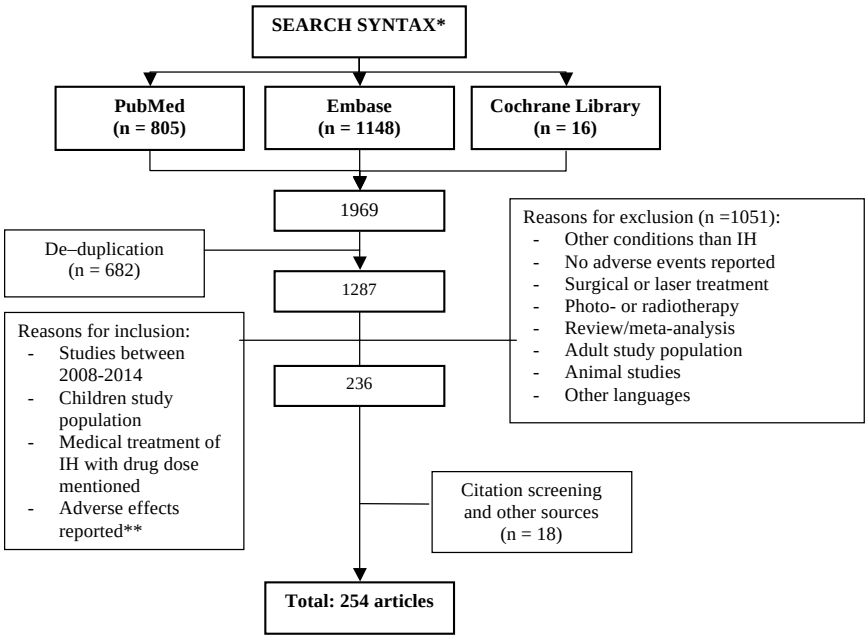

Fig 1 Flowchart according to the four-phase flow diagram of PRISMA
IH: infantile hemangioma
* Date of search: April 2014.
**When full text was not available, but all necessary information (i.e. number of patients, medicine, dose, adverse events) was listed in the abstract, this particular publication was included.

Patients and treatment

In these 254 studies a total of 10,022 patients were included (Table 1). All references are available as an online supplement. Six studies were case-control or retrospective comparative studies (3%), 2% were randomized controlled trials (n=4 level I, n=2 level II) and all other were case reports and case series from retrospective or prospective cohorts (level III and IV). From the included studies, subgroups of patients were made to deduct combination therapy from single-agent therapy. In total 285 studies were revealed, with single agents in 254 studies (n=9172 patients), covering five different treatment groups for IH (beta-blockers, corticosteroids, angiotensin-converting enzyme (ACE) inhibitors, immune modulators and chemotherapy). Combination therapy was found in 31 studies (n=850 patients). Therapies included oral, topical, intralesional and intravenous modalities. The number of patients in all studies ranged from 1 to 2013. Over 56% of all patients were treated with oral propranolol as a single agent (n=5621). Oral prednisone was used solitary in 722 patients (7%) and topical imiquimod in 709 patients (7%). All reported side effects and adverse events were stratified per drug, therapy modality and evaluated according to adult pharmacotherapeutic databases (Table 1 and 2). Some side effects and adverse events from therapy could not be found in these databases. Results from the former mentioned therapy groups used as a single agent (n=254 studies) are discussed in more detail.

Table 1 Summary review study details

Therapy	Dosage	No. Studies	No. Patients	Reported side and adverse effects
BETA-BLOCKER				
Propranolol (oral)	0,24-4 mg/kg/day	167	5621	(Arterial)(silent) hypotension, bradycardia, respiratory symptoms (bronchiolitis, dyspnea, bronchospasm, wheezing, noisy breathing, bronchial hyperreactivity, slower rate of breathing, bronchial asthma), gastro-intestinal problems, sleep disturbance, night terrors, tiredness, mood/behavioral changes, cold extremities, paleness, (silent) hypoglycemia, skin rash, exanthema or dry skin, eating problems (anorexia)#, vomiting, nausea, diarrhea, constipation, hyperkalemia, hyperphosphatemia because of tumor lysis syndrome#, mild right hemiparesis#, elevated alanine transaminase/aspartate transaminase or creatine kinase-MB levels#, abnormal electrocardiogram (not otherwise specified), prolonged sinus-arrest, hypertonia#, dental caries#, severe somnolence, profound mottling in lower legs, feet and hands#, flushing of face and hands, drowsiness, vascular endothelial growth factor (VEGF) decrease, seizure like episode, insomnia, agitation (irritability), delay in walking unassisted, breath holding spells, ulceration, cyanotic extremities, agranulocytosis, low body temperature, lethargy, somnolence, gastrointestinal upset, atypical events (change in neuroimaging: progressive vessel narrowing, change in neurologic status: mild hemiparesis), tissue necrosis, gastro-oesophageal reflux disease, no weight gain and death caused by acute renal failure after diarrhea
Propranolol (intralesional = IL)	0,2 ml/cm or 1 mg/ml propranolol solution	4	35	Local pain and redness#
Propranolol (topical)	1% balm/ointment	5	135	None
Propranolol + steroids	*(0.5-3 mg/kg/day propranolol and 1-3 mg/kg/day prednisolone if systemically used)*	*14*	*56*	*Hypoglycemia during tapering of prednisolone, bradycardia, mild hypotension, transient diarrhea, hypertension and growth retardation*
Propranolol (oral) + bleomycine		*1*	*1*	

Table 1 Summary review study details *(continued)*

Therapy	Dosage	No. Studies	No. Patients	Reported side and adverse effects
Nadolol (oral)	0,5-4 mg/kg/day	1	10	Sleep disturbance, irritability, cold extremities, gastrointestinal symptoms and fever
Acebutolol (oral)	2-10 mg/kg/day	2	7	None
Atenolol (oral)	0,5-1 mg/kg/day	5	80	Hypotension, sleep disturbance, constipation, diarrhea, cold extremities and vomiting
Brimodine / Timolol (topical)	*brimonidine 0.2% -timolol 0.5%*	*1*	*3*	*None*
Timolol (topical)	0,1-0,5%, 1-5x per day	20	511	Sleep disturbance. One study reported systemic uptake: 20/24 patients (83%) had positive urine tests for timolol. Crusting and scaring
CORTICOSTEROIDS				
Prednisolone (oral)	1-5 mg/kg/day, or 3-5 mg/kg/day every other day	20	722	Cushingoid appearance, growth restriction, (arterial) hypertension, hirsutism, increased appetite, increased weight, fever, infection, pneumonia, severe respiratory syncytial virus, oral thrush, hypercholesterolemia, restlessness, insomnia, irritability, skin atrophy, ulceration, acne, local inflammatory reaction, hypopigmentation, glucosuria, cortisone-induced brain atrophy inducing oculomotor palsy, behavioral changes (restlessness) accompanied by increased crying, temporary adrenal insufficiency, flushing and sweating
Triamcinolone (IL) (in combination with betamethasone IL or dexamethasone IL)	*0,2-1 ml/cm or 40mg/ml solution triamcinolone (4-8 mg dexamethasone)*	*12 (7 T and 5 T/D or T/B)*	*1166 (59 combination therapy)*	*Local: skin atrophy, ulceration, hypopigmentation, eyelid necrosis, hypopigmentation of the iris and ophthalmic artery occlusion. Systemic: Cushingoid appearance, failure to thrive, adrenal insufficiency with transient reductions of weight and linear growth, infection and hypertension*

Table 1 Summary review study details *(continued)*

Therapy	Dosage	No. Studies	No. Patients	Reported side and adverse effects
Triamcinolone (IL) + prednisolone (oral)	*prednisolone 1-2 mg/kg every other dauy and triamcinolone 1-2 mg/kg*	*2*	*629*	*Local: skin atrophy, ulceration, hypopigmentation and orbital cellulites. Systemic: hypertension, failure to thrive and infection*
Triamcinolon (IL) + propranolol (oral)		*1*	*1*	*None*
Bethametasone (IL)		1	36	Bruising at injection site
ACE-INHIBITORS				
Captopril (oral)	0,1-0,5 mg/kg 3 times/week	1	8	Transient mild creatinine elevation
IMMUNE MODULATORS				
Imiquimod cream	5%, 3-7 times/week	10	709	Local: erythema/edema, erosions, blister, itch, peeling, crusting, ulceration, scarring, (severe) inflammatory response, desquamation and secondary infection. Systemic: fever, nausea and diarrhea
Interferon alpha (injection)	3000000 U/m2/3 times a week	4	58	Fever, fatigue, retrosternal oppression, moderate hair loss, nausea, vomiting, flu like symptoms, hypertriglyceridemia and elevated liver enzymes
Interferon alpha (injection) + methylprednisolone (IV) + prednisolone (oral)	*0,3MU/m2/day, 30mg/kg/day and 2mg/kg/day respectively*	*1*	*1*	*None*
Prednisolone (oral) + interferon	*prednisolone: 2,5-4mg/kg/day*	*1*	*2*	*No remaining neurological damage*
Sirolimus	Blood levels ranged from 4.3 to 19.2 ng/ml (aimed levels range from 9 to 12 ng/ml)	1	1	Multiple times grade I/II hypertriglyceridemia, one episode of febrile neutropenia and transient episodes of mild mucositis or stomatitis

Table 1 Summary review study details *(continued)*

Therapy	Dosage	No. Studies	No. Patients	Reported side and adverse effects
CHEMOTHERAPY				
Bleomycin (IL)	8-15 mg or 0,5 mg/kg	3	123	Local: edema, swelling, ulceration, skin rash, bruising and cellulites Systemic: nausea, loss of appetite, headache and hyperpigmentation at electrocardiograph electrodes site
Bleomycin (IL) + dexamethasone (IL)	*2-8mg bleomycin*	*2*	*82*	*No severe adverse effects such as lung fibrosis or growth restriction*
Vincristine (if no response Vinblastine)	Vincristine: 0,025mg/kg or 1,5mg/m2 weekly. Vinblastine: 6-14mg/m2 weekly	2	8	Bacteremia with anemia, motor delay, peripheral neuropathy, cushingoid appearance# and tracheal fibrosis in child with subglottic IH#
Prednisolone (oral) + Vincristine	*Prednisolone: 3-5mg/kg/day. Vincristine: 0,025mg/kg/day weekly or 0,15-0,25mg/kg 8 weekly*	*2*	*9*	*Fever, sepsis, hypertension and central catheter infection#*
Cyclophosphamide	4 courses of 10 mg/kg/day of cyclophosphamide and 10 mg/kg/d of MESNA for 4 consecutive days, 10 days apart	1	1	Fever with positive hemoculture# and pleural infusion#
Propranolol (oral) + Vincristine + Steroids		*1*	*7*	*None*
Total		**285**	**10022**	

Italic: double agent therapy study

unknown adverse event according to adult pharmacotherapeutic database sources (see reference list main article)

IL: intralesional; IV: intravenous; MESNA: sodium-2-mercaptoethane sulfonate

Table 2 Treatment side and adverse events according to adult pharmacotherapeutic databases

Therapy	Side and adverse events	Comments
BETA-BLOCKER		
Propranolol (oral)	Regularly (1-10%): sleep disturbances, nightmares, bradycardia, cold extremities, Raynauds phenomena, shortness of breath, tiredness and inertia Occasionally (0.1-1%): diarrhea, nausea, vomiting Rarely (0.01-0.1%): thrombocytopenia, heart block, deterioration heart failure, orthostatic hypotension, syncope, angioedema, hallucinations, psychosis, mood swings, confusion, amnesia, dizziness, paresthesia, visual impairment, dry eyes, deterioration claudicatio intermittens, bronchospasms, skin rash, deterioration psoriasis, alopecia Extremely rare (<0.01%): deterioration angina pectoris or myasthenia gravis, hyperhydrosis, positive antinuclear antibody serology, agranulocytosis, masking thyreotoxicosis, changes in fat metabolism, hyoglycaemia, depression, headache, conjunctivitis, constipation, dry mouth, arthralgia, reduced renal function, impotence	
Propranolol (intralesional)		Intralesional therapy is not specified
Propranolol (topical)		Topical therapy is not specified
Nadolol (oral)	Bradyarrhythmia (2%), dizziness (2%), fatigue (2%), atrioventricular block (1%), cardiac dysrhythmia (1%) and heart failure (1%)#	
Acebutolol (oral)	Arthralgia, sleep disturbances, depression, visual hallucinations, dizziness, dry eyes, bradycardia, atrioventricular conduction prolongation, heart block, heart failure, hypotension, bronchospasms in patients with bronchial and asthmatic diseases, nausea, diarrhea, pruritus, cold extremities, fatigue and positive antinuclear antibody serology	
Atenolol (oral)	Regularly (1-10%): bradycardia, nausea, vomiting, diarrhea, tiredness and cyanotic extremities Occasionally (0.1-1%): sleep disturbances, elevated transaminases Rare (0,01-0,1%): thrombocytopenia, leucopenia, Raynauds phenomena, hallucinations, psychosis, depression, confusion, dizziness, paresthesia, hypotension, aggravated heart failure, slow atrioventricular node conduction or increase in existing atrioventricular block, hepatotoxicity and bronchospasms, deterioration claudication intermittens, heart failure, headache, visual impairment, dry eyes, bronchospasms, dry mouth, hepatotoxicity, alopecia, impotence, thrombocytopenia Extremely rare (<0.01%): positive antinuclear antibody serology, urticaria, exanthema, angio-edema, masking symptoms of hypglycaemia and thyreotoxicosis	

Table 2 Treatment side and adverse events according to adult pharmacotherapeutic databases *(continued)*

Therapy	Side and adverse events	Comments
Timolol (topical)	Occasionally (0,1-1%): asthenia, dizziness, depression, headache, respiratory problems, nausea, dyspepsia, bradycardia and syncope Rarely (0,01-0,1%): hypotension, palpitation, insomnia, nightmares, amnesia, deterioration myasthenia gravis, tinnitus, dry mouth, diarrhea, decompensatio cordis, Raynauds phenomena, edema, cough, alopecia, hypoglycaemia, urticaria, chest pain, skin rash, arrhythmia, heart block, cardiac arrest, positive antinuclear antibody serology, cerebral ischemia and heart failure*	*Reported side effects with the use of timolol *eye drops*
CORTICOSTEROIDS		
Prednisolone (oral)	Regularly (1-10%): leukocytosis, lymphopenia, polycythemia, immunosuppression, masking infections, sodium retention, adrenal insufficiency, Cushing's syndrome, potassium excretion, increased appetite, increase in weight, diminished glucose tolerance, hypercholesterolaemia, hypertriglyceridemia, insomnia, headache, telangiectasia, petechia, bruising, muscle atrophy, muscle weakness, osteoporosis Occasionally (0,1-1%): hypertension, atherosclerosis, thrombosis, vasculitis, ulcus pepticum, acne, changed skin pigmentation Rarely (0,01-0,1%): allergic reactions, amenorrhoea, disturbed thyroid function, depression, mood changes, psychosis, increase of intracranial pressure with papilledema, pancreatitis, aseptic bone necrosis, tachycardia, hypopotassaemic alkalosis, nausea, vomiting, diarrhea, hirsutism, sepsis, heart failure, failure to thrive, convulsion, vertigo, decreased carbohydrate tolerance, hypertrophic cardiomyopathy in low birth weight children, lymphocyto- and eosinophilopenia	Frequencies are specified.
Triamcinolone (intralesional)		Not specified in *intralesional* triamcinolon
Bethametasone (intralesional)		Intralesional therapy with bethametasone is not specified
ACE-INHIBITORS		
Captopril (oral)	Regularly (1-10%): dyspnea, vomiting, nausea, diarrhea, constipation, stomach ache, altered taste, dizziness, sleep disturbances, skin rash, pruritis, alopecia, weight loss, dry cough and dizziness Occasionally (0,1-1%): tachycardia, tachyarrhythmia, angina pectoris, chest pain, palpitation, flushing, malaise, tiredness, Raynauds phenomena, paleness, angio-edema and hypotension Rarely (0,01-0,1%): renal failure, anorexia, headache, paresthesia, stomatitis Extremely rare (<0,01%): neutropenia, agranulocytosis, pancytopenia, anemia, thrombocytopenia, lymphadenopathy, eosinophilia, auto-immune disorders, elevated potassium, hypoglycaemia, depression, anaphylactic reactions, cardiac arrest, cerebrovascular accident, fever, myalgia, gynaecosmasthia, nephrotic syndrome, liver insufficiency, pancreatitis, positive antinuclear antibody serology, urticaria, visual impairment, glossitis, confusion, ulcus pepticum, alveolitis and Stevens Johnson syndrome	

Table 2 Treatment side and adverse events according to adult pharmacotherapeutic databases *(continued)*

Therapy	Side and adverse events	Comments
IMMUNE MODULATORS		
Imiquimod cream	Frequently (>10%): local pain and inflammation, paresthesia, pruritis and skin reaction Regularly (1-10%): headache, infection, asthenia, lymphadenopathy, anorexia, dizziness, migraine, depression and severe local skin reaction. Increased liver enzymes, decreased number of hemoglobulin, leucocytes or thrombocytes Occasionally (0,1-1%): flu-like symptoms, gastro-intestinalcomplaints, anorexia, tinnitus, flushing, rhinitis, pharyngitis, arthralgia, alopecia, altered pigmentation, elevation liver enzymes, pancytopenia	
Interferon alpha (injection)	Frequently (>10%): hypo- and hypertension, cyanosis, diarrhea, alopecia, nausea, arrhythmia, palpitations, chest pain, flu-like symptoms, anorexia, leucopenia and hypocalcemia Regularly (1-10%): trombocytopenia, anemia, dry mouth, vomiting, stomachache, edema and weight loss Occasionally (0,1-1%): electrolyte disturbance, dehydration, depression, anxiety, mental function changes, confusion, behavioral changes, amnesia, neuropathy, dizziness, paresthesia and vertigo Rarely (0,01-0,1%): pneumonia, agranulocytosis, hemolytic anemia, auto-immune disorder, acute hypersensitivity reaction, diabetes mellitus, hyperglycemia, hyper- or hypothyroidism, suicide (attempt), coma, conjunctivitis, visual impairment, pruritis, convulsions, cardiac or respiratory arrest, myocardial infarction, congestive heart failure, pulmonary edema, dyspnea, hypertension, hypotension, proteinuria vasculitis, liver or renal failure and cerebrovascular events Extremely rare (<0,01%): idiopathic thrombocytopenic purpura and sarcoidosis	Side effect described with the use of interferon alfa 2A
Sirolimus (oral)	Common (>10%): thrombocytopaenia, anaemia, pyrexia, hypertension, hypokpotassemia, hypophosphatemia, urinary tract infection, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, abdominal pain, lymphocele, peripheral edema, arthralgia, acne, diarrhea, pain, constipation, nausea, headache, increased blood creatinine and increased blood lactate dehydrogenase (LDH) Regularly (1-10%): diabetes mellitus, bacterial/fungal and viral infections, sepsis, edema, bone necrosis, epistaxis, skin rash, skin cancer, leucopenia, neutropenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, tachycardia, venous thrombosis, interstitial pulmonary disease, tachycardia, pleural effusion, stomatitis, ascites, abnormal liver function, proteinuria, amenorrhoea, menorrhagia Occasionally (0.1-1%): lymphoma, lymphoprolipherative disease, pancytopenia, pancreatitis, nephrotic syndrome, pulmonary bleeding, pulmonary embolism, pericardial effusion Rarely (0.01-0.1%): lymphedema, alveolar proteinosis, anaphylaxis, angioedema, dermatitis and allergic vasculitis	
CHEMOTHERAPY		
Bleomycine (intralesional)	Frequently (>10%): damage to skin or mucous membranes (50%), fever after first injection, interstitial pneumonia (10%), which can lead to irreversible lung fibrosis and has a 1% mortality rate* Regularly (1-10%): severe hypersensitivity reaction (1%) Occasionally (0,1-1%): minor bone marrow suppression and minor thrombocytopenia Rarely (0,01-0,1%): hypotension, hyperpyrexia, vascular damage, such as myocardial infarction, disturbed blood flow in the brain, coronary heart disease or hemolytic uremic syndrome. Possible effects: local thrombophlebitis and vein occlusion after intravenous injection. Hyperparesthesia, anorexia and weight loss	*pulmonary complications were not seen in patients using bleomycine for local therapy

Table 2 Treatment side and adverse events according to adult pharmacotherapeutic databases *(continued)*

Therapy	Side and adverse events	Comments
Vincristine (intravenous)	Frequently (>10%): neurotoxicity, such as peripheral neuropathy, decreased reflexes, paresthesia, neuralgia, muscle weakness, atactic gait and cranial nerve damage Regularly (1-10%): constipation, transient thrombocytosis, acute dyspnea and bronchospasm and potentially life threatening vocal cord paralysis Occasionally (0,1-1%): severe bone marrow suppression, coronary artery disease, myocardial infarction, paralytic ileus, confusion, depression, psychosis, hallucinations, hyperuricemia and convulsions with hypertension which can result in coma. At injection site: phlebitis, cellulites or necrosis Rarely (0,01-0,1%): hyper- or hypotension, fever, headache, intestinal necrosis or perforation, hepatic veno-occlusive disease, inappropriate anti-diuretic hormone (ADH) secretion syndrome and hypersensitivity response	
Vinblastine (intravenous)	Frequently (>10%): leucopenia, paresthesia, peripheral neuropathy, nausea, vomiting and alopecia Regularly (1-10%): anemia, thrombocytopenia, myelosuppression, pharyngitis, dyspnea, constipation, ileus, gastric bleeding from ulcer, hemorrhagic enterocolitis, rectal bleeding, anorexia and diarrea Occasionally (0,1-1%): depression, hypertension, (orthostatic) hypotension, tumor pain and general discomfort Rarely (0,01-0,1%): inappropriate anti-diuretic hormone (ADH) secretion syndrome, sensibility disturbances, peripheral neuritis, headache, convulsions, dizziness, ototoxicity, vestibular and auditive damage of the cranial nerve with deafness, disorder in balance with dizziness, nystagmus and vertigo, sinustachycardia, angina pectoris, atrioventricular block, arythmia and skin blistering Extremely rare (<0,01%): hemolytic anemia, psychosis, erosion of eye epithelia with blepharospams, swelling of the eye lid, pre-auricular lymphnodes swelling after contact with the cornea, tinnitus, stomatitis, stomach ache, sensitive auricular lymphnodes, liver fibrosis, dermatitis, phototoxicity, muscle atrophy, urine retention, thrombotic microangiopathy with renal insufficiency, infertility, aspermia, general weakness and fever. In case of extravasation: cellulitis, necrosis, thrombophlebitis and pain at the injection site	
Cyclophosphamide (intravenous)	Frequently (>10%): myelosuppression, alopecia, fever, (hemorrhagic) cystitis and hematuria Regularly (1-10%): infection, mucositis, asthenia, malaise, rigor Occasionally (0,1-1%): sepsis, neuropathy, allergic reactions, thrombocytopenia, anemia, anorexia, cardiomyopathy, myocarditis, heart failure, tachycardia and ECG changes Rarely (0,01-0,1%): myelodysplastic syndrome, secondary malignancies, visual impairment, skin rash, chest pain, dehydration, bleeding, convulsions, (supra) ventricular arrhythmia, liver function disorders and hepatitis Extremely rare (<0,01%): tumor lysis syndrome, disseminated intravascular clotting, haemolytic uremic syndrome, inappropriate anti-diuretic hormone (ADH) secretion syndrome, ventricular fibrillation, hypo- or hypertension, renal insufficiency, dizziness, paresthesia, conjunctivitis, ventricular/atrial fibrillation, pericarditis, hypertension, hypotension, dyspnea, stomatitis, veno-occlusive disease and multi organ failure	

Sources: http://www.cbg-meb.nl/

http://www.micromedexsolutions.com (January 2015) #

http://www.farmacotherapeutischkompas.nl

Beta-blockers

Propranolol

Two randomized trials were identified that supported efficacy of propranolol, one from the search and one while performing this study [12,13]. The nonselective lipophilic beta-receptor antagonist propranolol acts by inhibition of both beta-1 and beta-2 adrenoreceptors [14]. It is both effective during the proliferative and the involution phase of IH growth. The mechanism of action of propranolol in IH is not yet completely understood, but it is thought to originate from several effects, like vasoconstriction [2,15], inhibition of angiogenesis [16-23], stimulation of apoptosis [24] and inhibition of the renin-angiotensin-system (RAS) [25,26]. Adverse effects of oral propranolol reported in 167 studies varied from cardiovascular events, respiratory symptoms, gastro-intestinal problems, metabolic alterations, skin changes and central nervous system symptoms. Intralesional propranolol studies (n=4) showed symptoms due to pain at the injection site and redness of the skin, while topical propranolol studies (n=5) revealed no adverse effects.

Atenolol

Itinteang et al. suggested that propranolol acts via the renin-angiotensin system in regulating accelerated involution of proliferating IH by decreasing renin production in the kidneys [25]. As the kidneys predominantly express beta-1 receptors, the renin-angiotensine-aldosterone system (RAAS) is most likely one of the missing links in understanding the working mechanism of both beta-blockers and ACE inhibitors in the treatment of IH [27]. Atenolol is a hydrophilic beta-blocker, acting on beta-1 receptors with a proven efficacy in the treatment of IH [28,29]. Another explanation for the effect of atenolol could be the limited beta-2 blocking potential of atenolol [30]. In the studies used in this overview the reported side effects and adverse events noted were hypotension, sleep disturbance, constipation, diarrhea, cold extremities and vomiting.

Timolol

Timolol is a non-selective lipophilic beta-blocker that is comparable to propranolol in mechanism of action. While timolol is available as a liquid gel it can be topically administered to superficial IH as can propranolol cream [31]. Topical application reveals limited systemic absorption, and therefore, systemic side effects and adverse events are uncommon. However, Weibel et al. showed that 83% of children treated with topical timolol had urinary timolol excretion, suggestive of systemic uptake [32]. One study reported sleeping disturbance in one patient which is also suggestive of systemic side effects of topical administration [33]. One randomized trial with 41 patients with superficial IH revealed effectiveness of timolol without significant differences in heart rate or blood pressure measurements compared to placebo [34].

Corticosteroids

Although corticosteroids have been the basis of treatment in IHs for half a century, little is known about the exact working mechanism in infantile hemangiomas. It is suggested that dexamethasone suppresses vasculogenesis of hemangioma-derived stem cells in vitro and corticosteroids diminish secretion of vascular endothelial growth factor (VEGF)-A from these stem cells in vitro [35] . A decrease in VEGF-A can sufficiently suppress vasculogenesis of hemangioma-derived stem cells in vivo. Corticosteroids are not able to suppress VEGF-A if it is from hemangioma-derived *endothelial* cells from human umbilical cords [35]. VEGF-A was detected in the proliferative phase of IH, but not in the involution phase. This might explain why corticosteroids are most effective during the proliferative phase of the IH. Corticosteroids can be used systemically, intralesional and as a topical treatment for IH. One randomized trial is known for the effectiveness of corticosteroids in IH in comparison to propranolol versus both [36]. The conclusion was that prednisolone was associated with a higher number of complications, thereby decreasing patient compliance. Propranolol showed a consistent, rapid therapeutic effect compared to prednisolone. A combination of the two had a comparable but not superior efficacy than propranolol alone. Another randomized controlled trial by Baumann et al revealed a similar efficacy of both drugs [37]. Prednisolone showed a faster response rate while propranolol was better tolerated with significantly fewer severe short-term adverse events. In this review side effects and adverse events of systemically used corticosteroids were seen in 20 studies with a total of 722 patients and included symptoms of metabolic, cardiovascular, endocrine, gastro-intestinal, infectious, respiratory, central nervous system and dermatological origin. Intralesional corticosteroid therapy showed local skin symptoms varying from skin atrophy to necrosis but it also revealed systemic side effects and adverse events (cushingoid appearance, failure to thrive, adrenal insufficiency with transient reductions of weight and linear growth, infection, hypertension).

ACE-inhibitors

The RAAS is involved in the proliferative phase of IH growth. This is supported by the observation of the negative action of propranolol on renin or the suppression of ACE by ACE-inhibitors like captopril. Both actions result in diminished production of angiotensin 2 and a subsequent regression of IH [25]. Sinaiko et al. found elevated levels of renin in children treated with ACE-inhibitors, suggesting that suppression of renin by beta-blockers in addition to ACE-inhibition creates an even larger effect on IH regression [25,38]. No further evidence in literature could be found for this therapy. Adverse effects in this overview came from one study with 8 patients showing a transient mild creatinine elevation in the first week of treatment in one of the patients [27].

Immune modulators

Imiquimod (topical)

Imiquimod is known to influence the immune system by induction of cytokine synthesis and thereby stimulating secretion of cytokines from macrophages, monocytes and keratinocytes in the epidermis. These cytokines, interferon (IFN), tumor necrosis factor alpha and interleukins (IL) lead to a reduction of pro-angiogenic factors, cell death in endothelial cells and to a decreased tumor invasion and cell motility [39]. Furthermore, IL-12 is known for its inhibition of the angiogenesis in vivo and tube forming of endothelial cells in vitro [40]. Studies in mice revealed that imiquimod could result in a decreased activity of matrix metalloproteinase-9 [39]. Therefore, the mechanism of action of imiquimod is ascribed to a cascade that results in the synthesis of cytokines that inhibit growth of IH [41]. We identified no evidence-based trials in IH. We included 10 papers with in total 709 IH patients treated with imiquimod. Adverse effects reported were both local skin reactions and systemic symptoms of fever and gastro-intestinal complaints.

Interferon-alfa

Interferon-alfa (INF- α) is a cytokine, which suppresses the growth of IH by inhibition of angiogenesis [42]. In IH, INF-α -2a and -2b are used subcutaneously. INF- α influences vessel growth by diminishing the fibroblast growth factor production or down regulation of IL-8 and the VEGF gene expression. INF- α acts on the endothelial cells directly by both impairment of proliferation and migration. Indraccolo et al, reported that INF- α reduces gene expression of endothelial cells and thereby contributing to an increase of negative regulators of angiogenesis [43]. In 58 patients using INF- α injections for IH several adverse effects were reported; gastro-intestinal, metabolic disturbances but also general symptoms such as fever, fatigue, hair loss and flu-like symptoms.

Sirolimus

Mammalian target of rapamycin (mTOR) acts as a master switch for numerous cellular processes including angiogenesis and cell growth [44]. Sirolimus is a mTOR inhibitor and could therefore be beneficial in the treatment of vascular anomalies [45]. In a case report with only one patient several side effects and adverse events occurred (hypertriglyceridemia, febrile neutropenia and mild mucositis) [46].

Chemotherapy

Bleomycin (intralesional)

Bleomycin is a cytotoxic agent, which is able to degrade deoxyribonucleic acid (DNA), which results in an inhibition of cell replication, cell growth and DNA-synthesis in tumor biology. It is used for intralesional treatment in IH. This sclerosing agent acts on vascular endothelium by induction of cell-injury and disperse endothelial cells, leading to occlusion of blood vessels. Overall, it stimulates apoptosis of rapidly dividing cells, as is seen in proliferating IH [47]. The literature is limited for retrospective and prospective case studies only. In three studies of bleomycine-only intralesional therapy for IH, side effects and adverse events in 123 patients consisted of local symptoms at the injection site, but also systemic gastro-intestinal complaints.

Vincristine

The vinca-alkaloid vincristine is known for its systemic chemotherapeutic action in malignancies. It negatively influences vascular and endothelial cell growth, inducing apoptosis and is furthermore able to stop mitosis by inhibiting the formation of microtubules [48]. Evidence based trials with vincristine in IH are not available. Vincristine was used in 2 reports with 8 patients of IH and reported side effects were due to infectious and peripheral nervous system origin.

Cyclophosphamide

Cyclophosphamide is an alkylating agent affecting DNA and the cell cycle process. It is furthermore known for its immunosuppressive effect on B and T cells [6]. One case with diffuse neonatal hemangiomatosis was treated with cyclophosphamide and suffered from fever, sepsis, catheter infection and hypertension [49].

Discussion

A proper diagnosis of IH should be obtained before starting any therapy. Although this statement is beyond the scope of this report, it is especially true for initiating systemic therapy for IH with potential side and adverse effects. This review focuses specifically on reported side effects and adverse events of any medical treatment strategy in IH. This comprehensive overview of literature was performed by stratification of all reported side effects and adverse events per drug and treatment modality instead of by frequencies in patients. The outcome demonstrates that IH are treated with a wide range of medications. In total 10.022 patients treated in five different single treatment medication groups for IH were included. Randomized controlled trails have only scarcely been performed for any of

the reported treatment strategies. Short and long-term side and adverse effects are even less well studied. Pharmacotherapeutic databases are incomplete in information regarding the treatment options in children with IH.

Corticosteroids are well known for their adverse effects and are therefore no longer considered a first-line treatment in pediatric IH. Beta-blockers have become the first-line treatment modality for complicated hemangiomas. They appear to be more successful than corticosteroids, also beyond the proliferative phase [50], while they have less side effects, although short and especially long-term adverse events are not systematically studied. The lipophilic non-selective character of propranolol causes cardiovascular, respiratory and central nervous system adverse effects. While the hydrophilic and more selective beta-blocker atenolol is a promising alternative, its efficacy, side effects and adverse events spectrum has not been studied as extensively yet [27-29,51-53]. Topical beta-blocker treatment possibly has less systemic adverse effects but it seems to be effective only in superficial IH [31]. ACE-inhibition seems to be a good alternative by its action mechanism although literature is very limited and renal adverse effects at young age can be harmful [27]. Chemotherapy and immune modulator therapies have also been studied but are known for serious side effects and are currently replaced by less harmful strategies, that appear to have at least similar effectiveness.

Table 3 and 4 show effective therapies in children with IH, according to literature with dosage, pretreatment and treatment strategies. In addition, they depict common, unusual, serious and harmless side effects and adverse events. This overview might be helpful for the treating physician making a deliberate individualized or case-based choice for any patient with complicated IH according to current knowledge at any point during treatment. Moreover, we hope this review will be an impetus for further research, since especially long-term side effects in this young patient population are unknown. While table 3 focuses on first and second-line therapy, table 4 shows therapies which should only be used in case of severe complicated IH not responding to first or second-line therapy. After consulting a vascular expert team first line therapy can be used in general practice, according to a standardized protocol. Second and third line therapy for IH though should be indicated and coordinated by a multidisciplinary team with expert knowledge on vascular abnormalities in children. Systemic immune modulator and chemotherapy medication are currently only indicated in severe complicated IH not responding to any other treatment and should exclusively be under team expert auspices. In absence of evidence based literature it is hard to judge the most efficacious and safest therapy from the reviewed options.

Table 3 Recommendations for first and second-line therapy for IH

Drug	Advised dosage	Pretreatment evaluation	Contra-indications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side and adverse effects
Source	Literature review	Dutch pediatric formulary # and propranolol guideline *	Dutch pediatric formulary		Literature review and/or pharmacotherapeutic databases^ if >1%	Pharmacotherapeutic databases
BETA-BLOCKER						
Propranolol (oral)	2-3 mg/kg/day	Blood pressure (BP) and heart rate (HR), cardiac (family) history, electrocardiogram (ECG) in children at risk	Sinus bradycardia, atrioventricular (AV) block, hypotension, respiratory disorders, heart failure, adrenal insufficiency and hypoglycaemia	Clinical evaluation (ie. history taking and physical examination)	Bradycardia, hypotension, cyanotic/cold extremities, sleep disturbance, gastro intestinal symptoms and bronchospasm, tiredness and inertia	Heart block, heart failure, hypotension, hypoglycemia, depression and agranulocytosis
Atenolol (oral)	1-2 mg/kg/day	BP + HR, Cardiac (family) history, ECG in children at risk	Sinus bradycardia, sick sinus syndrome, AV block, hypotension, respiratory disorders, heart failure, pheochromocytoma and hypoglycaemia	Clinical evaluation	Bradycardia, hypotension, cyanotic extremities, sleep disturbances, tiredness and gastro intestinal symptoms	Thrombocytopenia, leucopenia, psychosis, depression, aggravated heart failure, slow AV node conduction or increase in existing AV block and hepatotoxicity
Timolol (topical)	0.1-0.5% 1-5 times a day	BP + HR, Cardiac (family) history, ECG in children at risk	Asthma and other chronic pulmonary disorders, sinus bradycardia, sick-sinussyndrome, AV block hart failure, cerebrovascular insufficiency, Raynauds phenomenon, diabetes mellitus, hypoglycaemia and myasthenia gravis	Clinical evaluation for risk of systemic uptake	Sleep disturbance	Asthenia, depression, bradycardia, respiratory problems, syncope, hypotension, chest pain, arrhythmia, heart block, cardiac arrest, cerebral ischemia and heart failure

Table 3 Recommendations for first and second-line therapy for IH *(continued)*

Drug	Advised dosage	Pretreatment evaluation	Contra-indications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side and adverse effects
CORTICOSTEROIDS						
Prednisolone (oral)	1-5 mg /kg /day, or 3-5 mg/kg/day every other day		Ulcus ventriculi or duodeni and acute infections	Clinical evaluation, growth and blood pressure	Cushing's syndrome, adrenal insufficiency, hypertension, sodium retention, potassium excretion, teleangiectasia, hypercholesterolaemia, leukocytosis, lymphocytopenia, polycythemia, immunosuppression, diminished glucose tolerance, insomnia, headache, muscle weakness/atrophy, osteoporosis, failure to thrive and weight gain	Immunosuppression, sepsis, heart failure, adrenal insufficiency, muscle athrophy, osteoporosis, increase of intracranial pressure with papilledema, personality or mood changes, thrombo-embolism, hypertrophic cardiac myopathy in low birth weight children, pancreatitis, gastric ulcer and lymphocytopenia
Triamcinolone (intralesional)	0,2-1ml/cm or 40mg/ml solution triamcinolone		Hypersensitivity, ulcus ventriculi or duodeni, infections, glucocorticoïd induced myopathy, emotional unstable, psychosis, psychiatric disorders, colitis, diverticulitis, hypertension, osteoporosis and myasthenia gravis	Clinical evaluation, growth and blood pressure	*Not specified in intralesional* triamcinolon. Systemic side effects comparable with oral steroids added with local side effects: Cushingoid appearance, failure to thrive and hypertension Local: skin atrophy and hypopigmentation	Eyelid necrosis, hypopigmentation of the iris, ophthalmic artery occlusion, ulceration, adrenal insufficiency and infection

Kinderformularium at https://www.kinderformularium.nl
* Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013;131:128-140.
^ Farmacotherapeutisch Kompas at http://www.farmacotherapeutischkompas.nl.
Summary of product characters (SmPCs) available at http://www.cbg-meb.nl/cbg/nl.
Informatorium Medicamentorum (Dutch manual for medicins).
Micromedex at www.thomsonhc.com (American online medicin database).
Meyler's Side Effects of Drugs. The International Encyclopedia of Adverse Drug Reactions and Interactions. 15th edition. Editor: JK Aronson.
AV:atrioventricular; BP: blood pressure; ECG: electrocardioagram; HR: heart rate

Table 4 Recommendations in complicated IH not responding to first or second-line therapy for clinicians in vascular expert teams

Drug	Advised dosage	Pretreatment evaluation	Contra-indications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side and adverse effects
Source	Literature review	Dutch pediatric formulary #	Dutch pediatric formulary		Literature review and/or pharmacotherapeutic databases^ if >1%	Pharmacotherapeutic databases
ACE-INHIBITORS						
Captopril (oral)	0,1-0,5 mg/kg three times a day	Renal function test	Renal failure or insufficiency, Angio-edema and caution for use in neonates	Clinical evaluation, weight, serum creatinine levels and blood count	Dyspnea, weight loss, gastro-intestinal complaints, sleep disturbances, alopecia, skin rash, pruritis, dry cough and dizziness	Tachyarrhythmia, angina pectoris, chest pain, hypotension, renal failure, neutropenia, anemia, thrombocytopenia, ulcus pepticum, lymphadenopathy, auto-immune disorders, liver insufficiency and Stevens Johnson syndrome
IMMUNE MODULATORS						
Imiquimod (topical)	5%, 3-7 times/week		Immunocompromised patients, auto-immune disorders and post-transplant patients	Clinical evaluation, serum blood count and liver enzymes	Local pain and inflammation, paresthesia and skin reaction, headache, infection, asthenia, dizziness, lymphadenopathy, anorexia, migraine, depression, severe local skin reaction. Increased liver enzymes, decreased hemoglobin and number of leukocytes and thrombocytes	Asthenia, lymphadenopathy, anorexia, depression, increased liver enzymes, decreased hemoglobin and number of leucocytes or thrombocytes

Table 4 Recommendations in complicated IH not responding to first or second-line therapy for clinicians in vascular expert teams *(continued)*

Drug	Advised dosage	Pretreatment evaluation	Contra-indications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side and adverse effects
Interferon-alpha (injection)	3000000 U/m2 3 times/week	Thyroid, renal and liver function tests	Severe cardiac disorder, liver of renal failure, epilepsy or central nervous disorders, history of auto-immune disorders or transplantations, unmanaged thyroid dysfunction and severe psychiatric history with depression or suicide attempt	Clinical evaluation for mood changes, blood pressure and serum electrolytes, glucose, triglycerids, thyroid and renal function, blood count and liver enzymes	Hypo- and hypertension, cyanosis, arrhythmia, palpitations, chest pain, flu-like symptoms, nausea, fatigue, anorexia, diarrhea, alopecia, leucopenia, hypocalcemia, thrombocytopenia, anemia, dry mouth, vomiting, stomachache, edema and weight loss.	Hypo- and hypertension, cyanosis, arrhythmia, chest pain, leucopenia, hypocalcemia, trombocytopenia, anemia, weight loss, electrolyte disturbance, dehydration, depression, mental function changes, behavioral changes, amnesia, neuropathy, paresthesia, pneumonia, agranocytosis, hemolytic anemia, auto-immune disorder, acute hypersensitivity reaction, diabetes mellitus, hyper- or hypothyroidism, suicide (attempt), coma, convulsions, cardiac or respiratory arrest, myocardial infarction, congestive heart failure, pulmonary edema, dyspnea, vasculitis, liver or renal failure, cerebrovascular effects and sarcoidosis
Sirolimus (oral)	Aimed levels range from 9 to 12 ng/ml		Hyperlipidemia, infections and post transplant patients	Clinical evaluation for mucositis, blood pressure, and serum level of sirolimus, electrolytes, creatinine, LDH, liver function, triglycerids, blood count, urine protein excretion Add pneumocystis jirovecii prophylaxis	Febrile neutropenia, infection, mucositis or stomatitis, leucopenia, thrombocytopenia, anemia, pyrexia, hypertension, electrolyte disturbances, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, abdominal pain, lymphocoele, peripheral oedema, arthralgia, acne, diarrhea, pain, skin rash, constipation, nausea, headache, increased blood creatinine and increased blood lactate dehydrogenase (LDH) bone necrosis, interstitial pulmonary disease, abnormal liver function, proteinuria, hemolytic uremic syndrome, venous thrombosis, tachycardia	Thrombocytopaenia, anemia, hypertension, hypokalemia, urinary tract infection, pneumonitis, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, increased blood creatinine, febrile neutropenia and stomatitis

Table 4 Recommendations in complicated IH not responding to first or second-line therapy for clinicians in vascular expert teams *(continued)*

Drug	Advised dosage	Pretreatment evaluation	Contra-indications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side and adverse effects
CHEMOTHERAPY						
Bleomycin (intralesional)	8-15 mg or 0,5 mg/kg		Acute lung infection, strongly decreased function or circulatory problems of the lungs and ataxia telangiectasia	Clinical evaluation	Damage to skin or mucous membranes, fever after first injection, severe hypersensitivity reaction, nausea and headache	Hypotension, hyperpyrexia, vascular damage, such as myocardial infarction, disturbed blood flow in the brain, coronary heart disease or hemolytic uremic syndrome, local thrombophlebitis and vein occlusion after intravenous injection and hyperparesthesia
Vincristine (intravenous)	0,025mg/kg or 1,5mg/m2 weekly	Liver function test	Severe liver function disorders, risk of ileus, radiotherapy including the liver and hypersensitivity of vinca alkaloids	Clinical evaluation for constipation, neurologic examination and serum blood count	Neurotoxicity, such as peripheral neuropathy, decreased reflexes, paresthesia, neuralgia, muscle weakness, atactic gait and cranial nerve damage, constipation, transient thrombocytosis, acute dyspnea and bronchospasm and potentially life threatening vocal cord paralysis	Neurotoxicity, such as peripheral neuropathy, decreased reflexes, paresthesia, neuralgia, muscle weakness, atactic gait and cranial nerve damage, acute dyspnea and bronchospasm, potentially life threatening vocal cord paralysis, severe bone marrow suppression, coronary artery disease, myocardial infarction, paralytic ileus, confusion, depression, psychosis, hyper- or hypotension, fever, intestinal necrosis or perforation, hepatic veno- occlusive disease, inappropriate ADH syndrome, hypersensitivity response, hyperuricemia and convulsions with hypertension which can result in coma. At injection site: phlebitis, cellulitis or necrosis

Table 4 Recommendations in complicated IH not responding to first or second-line therapy for clinicians in vascular expert teams *(continued)*

Drug	Advised dosage	Pretreatment evaluation	Contra-indications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side and adverse effects
Cyclophos-phamide (intravenous)	4 courses of 10 mg/kg / day with MESNA for 4 consecutive days, 10 days apart.	Analyze electrolyte disturbances, liver and renal function, urinating problems and exclude cystitis before initiation	Bone marrow suppression, bladder disorders, lower urinary tract obstruction or active infections, diabetes mellitus, diminished liver or kidney function, radiotherapy treatment and cardiac disorders	Clinical evaluation, serum blood count and urine erythrocytes sampling	Myeolosuppression, fever, alopecia, mucositis, asthenia, malaise, rigor, (hemorrhagic) cystitis, hematuria and infection	Myeolosuppression, (hemorrhagic) cystitis, hematuria, sepsis, neuropathy, cardiomyopathy, myocarditis, heart failure, tachycardia, myelodysplastic syndrome, secondary malignancies, convulsions, (supra) ventricular arrhythmia, liver function disorders, hepatitis, tumor lysis syndrome, disseminated intravascular clotting, haemolytic uremic syndrome, inappropriate anti-diuretic hormone (ADH) secretion syndrome, ventricular fibrillation, hypo- or hypertension, renal insufficiency and multi organ failure

Kinderformularium at https://www.kinderformularium.nl
^ Farmacotherapeutisch Kompas at http://www.farmacotherapeutischkompas.nl.
Summary of product characteristics (SmPCs) available at http://www.cbg-meb.nl
Informatorium Medicamentorum (Dutch manual for medicins).
Micromedex at www.thomsonhc.com (American online medicin database).
Meyler's Side Effects of Drugs. The International Encyclopedia of Adverse Drug Reactions and Interactions. 15th edition. Editor: JK Aronson.
ADH: antidiuretic hormone; LDH: lacatate dehydrogenase

The results of the conducted review has limitations by the low levels of evidence of included studies, small sample size for some therapy modalities, lack of available data on especially systematically studied side effects and adverse events and absence of longitudinal follow-up studies. Current review shows the side effects and adverse events listed by therapy without any denominator, which is a limitation that might leave the clinician with many uncertainties. Possibly also side effects and adverse events are underreported by this conducted review analysis. Furthermore propranolol is offered to a much larger population than corticosteroids ever were, which is reflected in this overview and accounts for an unsolved bias. Limitations in the use of pharmacotherapeutic databases were due to lack of information about specific treatment options for IH and the fact that derived information is from treated adults mostly for other indications. Several of the observed side effects and adverse events in the pediatric IH population are not reported in adult pharmacotherapeutic databases. This shows that the available databases currently are incomplete and should be updated. This is of importance to all professionals participating in the care of IH patients.

In conclusion there is a wide range of seemingly effective medical therapies for IH, although high level of evidence is still limited. Therapies utilized, demonstrate numerous side effects and adverse events merely known for their effect during therapy, while long-term outcome and sequelae are unknown in these patients. In order to guide the clinician to judge the most efficacious and safest therapy for an individual patient the list of therapeutic options for IH in children was reviewed. To date first line treatment in patients with IH is beta-blocker therapy. This approach is based on clinical observation, efficacy and tolerability of propranolol, especially in the short-term. Considering potential overuse of beta-blockers for uncomplicated IH and the uncertainty about long-term potential side effects and adverse events still makes critically weighing the treatment indication and more comprehensive review studies of great importance.

Expert opinion

The first- line approach with propranolol for IH seems to be predominantly based on clinical observation, efficacy and tolerability in the short-term. Only 7 years after the first report of Léauté-Labrèze et al [3], little is known about the long-term outcome and safety. The recently performed randomized controlled trial by Léauté-Labrèze, showed that propranolol was effective at a dose of 3 mg/kg/day for 6 months for IH (leaute-labreze et al. 2015). [13] It revealed a safety assessment by analysis of adverse events, which according to the authors included neurodevelopment revealed no notable differences between the propranolol treatment arms and the placebo group. Unfortunately the report does not specify in detail what variables were studied with regard to neurodevelopment and follow-up time was relatively short. The qualification of propranolol as a safe treatment strategy for

IH in pediatric patients should therefore be interpreted with caution.

To date, detailed assessment of cardiovascular, gross motor and neurocognitive development has not yet been published in IH patients treated with propranolol. Subsequently short- and long-term development outcome of treated infants with IH are unknown. Only one very recent study by Myakine et al, showed that in 103 patients with IH treated with propranolol no evidence of psychomotor developmental delay was found.[54] It remains possible though, the authors concluded, that propranolol treatment causes subtle adverse effects, which cannot be traced with tools such as the used van Wiechen scheme. And as such they suggest that future prospective studies using universal screening tools such as the Parents Evaluation of Develomental Status (PEDS), the Ages and Stages Questionnaire (ASQ) or more advanced neuropsychological tests are needed to support their findings. Kwon et al, reported on the analyses of infants treated with propranolol for various indications, including IH. [55] It demonstrated that no serious adverse events resulted in hospitalization and it supported the perceived safety profile of propranolol. Results also implied that serious adverse events might be delayed and thus not detected during initiation of the drug treatment. It is unknown whether young infants with IH and a normotensive cardiovascular system have a different complication risk of propranolol therapy compared to those infants treated with propranolol for cardiac indications. Data on long-term outcome of patients treated with beta-blockers for other indications than IH, for example patients with arrhythmic diseases, are lacking in literature. Another concern is the observation by Gonski, who noted that 4 of 84 IH patients with oral propranolol for IH demonstrated a delay in unassisted walking.[56] In support of this, Langley summarizes many associated CNS effects of propranolol, including a meta-analysis of Lonergan, showing propranolol treatment negatively influences recall of emotional material. [57,58]We endorse the concern raised by Langley about the unknown significance of CNS effects resulting from propranolol use in IH patients during early developmental stages and/or for prolonged periods of therapy. This concern is confirmed in adult literature revealing a reduction in subsequent memory for both new and previously learned emotional material and an impairment of mood and sleep quality by propranolol [58-60].

These findings suggest that this current therapeutic strategy needs to be updated with a thorough review of side effects and adverse events in short and especially long-term to judge beta-blocker therapy in its safety. The possibility to exchange the long-term sequelae of high-dose prednisone into acceptable short-term adverse events of propranolol seemed more important, than the unsolved ravels of possible long-term adverse events of propranolol. It is imperative that these unsolved ravels need thorough review during early developmental stages and especially in long-term follow-up studies to judge safety of propranolol. Moreover in absence of this information we are in favor of withholding propranolol therapy for pure cosmetic indications.

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Part III

Wide spectrum of pediatric vascular lesions

Chapter 7

Obstructive aortic arch pathology and infantile hemangioma: Coincidence or PHACES syndrome?

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Abstract

Objective: To determine the prevalence of PHACES syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects, Eye anomalies, Supra-umbilical raphe and/or Sternal pit) in patients with obstructive aortic arch pathology (OAAP) in order to achieve more insight in the possible association between infantile hemangiomas (IH) and cardiovascular anomalies.

Study design: Pediatric patients diagnosed with OAAP between 1999 and 2013 in our tertiary referral center were included. A questionnaire on the presence of an IH and other symptoms fitting the diagnostic criteria of PHACES syndrome was created. Deceased patients were analyzed separately.

Results: The questionnaire was sent to 266 patients with OAAP, of which 175 (66%) were returned. In 9 cases an IH was diagnosed. One child met the criteria of PHACES syndrome. This child demonstrated a segmental hemangioma and an atypical interrupted aortic arch with atresia of the left common carotid artery, which fits the complex vasculopathy seen in PHACES syndrome. The remainder (n=8) did not meet the PHACES criteria due to characteristics of IH or aortic arch. None of the deceased study objects fulfilled the PHACES syndrome criteria.

Conclusion: In this retrospective cohort, one child met the PHACES criteria, indicating that PHACES syndrome in OAAP patients is rare. Due to limited cohort size this study was underpowered to provide evidence of an association between IH and obstructive aortic arch pathology.

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Introduction

In 1978, Pascual-Castroviejo was the first to report coinciding anomalies (including congenital heart disease) in patients with cervicofacial hemangiomas. In view of the rarity of this combination Schneeweiss et al (1982) suggested a new syndrome of congenital cardiac and peripheral vascular anomalies. This association was further defined by Frieden et al (1996), where the acronym PHACE was introduced, later extended to PHACES with the 'S' reflecting supra-umbilical raphe or sternal pit. This syndrome includes Posterior fossa malformations, segmental Hemangiomas of the head and neck, Arterial anomalies, Cardiac defects, Eye anomalies and aforementioned ventral closure defects. Segmental hemangioma of the face or neck is the PHACES syndrome hallmark (Metry et al 2009, Metry et al 2009, Metry et al 2006 and Wendelin et al 2004). Cardiac involvement appears in 21 – 67% of PHACES syndrome patients [Metry et al 2009, Metry et al 2006, Haggstrom et al 2010, Metry et al 2001 and Bayer et al 2013). Aortic arch anomalies are the main cardiovascular feature, in particular coarctation of the aorta (AC), which is also associated with an increased risk of arterial ischemic stroke (AIS) [Metry et al 2009, Metry et al 2006, Metry et al 2001, Rao et al 2008, Bronzetti et al 2004, Giardini et al 2010, Siegel et al 2012 and Heyer et al 2008). In contrast to the few hundred patients reported with PHACES, infantile hemangiomas (IH) and congenital heart diseases are much more frequently diagnosed in children. The overall incidence of IH is estimated to be around 4 – 10% (Kilcline et al 2008, Jacobs 1976 and Hoornweg et al 2012), while AC has a birth prevalence of approximately 0.032%-0.036% worldwide as reported by Van der Linde et al (2011).

The pathophysiology of PHACES syndrome remains to be elucidated. A recent post-mortem study of Chad et al (2012) emphasizes the concept that an arteriopathy is the underlying defect in PHACES syndrome, resulting in dysplasia of large to medium sized arteries. From an embryologic point of view, the observation that left heart valve is absent in PHACES coarctation as mentioned by Bayer et al (2013) is supportive of this hypothesis. However, this does not directly explain the presence of hemangiomas, which are neoplastic rather than dysplastic anomalies. It is hypothesized that a delay or disturbance in the shift of embryonic to fetal vasculature might cause a hypoxic environment. Hypoxia subsequently might serve as a stimulus of IH development (Metry et al 2009 and Leaute-Labreze 2011). Current research focuses on a genetic basis for the vascular anomalies in PHACES patients. It is most likely that PHACES syndrome has a multifactorial origin with both genetic and environmental causes. In the future, large databases such as the 'PHACE registry' (http://www.phaceregistry.com/StudyInfo.html) might be able to either definitely prove an association between the several congenital cardiovascular defects and PHACES and to eludicate its genetic or multifactorial origin.

Most studies investigating PHACES phenomenon and the association with AC focused on patients that primarily had a (segmental) hemangioma. In sight of planning surgery for cardiac pathology, awareness of PHACES syndrome and its associated features is of in importance regarding for example, cerebral perfusion in PHACES patients. Because of the paucity of information from patients primarily diagnosed with AC, we performed a retrospective study in patients with obstructive aortic arch pathology (OAAP) in order to determine the prevalence of IH for the diagnosis PHACES syndrome in patients with aortic arch obstructions.

Methods

All pediatric patients referred to a tertiary referral centre for middle, south and east of the Netherlands between 1999 and 2013 were included. Patients were referred for diagnostic procedures or interventions (i.e. heart catherization and/or surgery) because of OAAP. OAAP was defined as AC, isolated hypoplastic aortic arch or interrupted aortic arch (IAA). A questionnaire focusing on presence of an infantile hemangioma and other symptoms in line with the diagnostic criteria of PHACES syndrome was constructed (available as online supplement). This survey including informed consent forms was sent to patients (aged > 16 years) or their parents (when aged < 16 years). Non-responders were reminded by mail one month later. When still not responding, they were reminded by telephone. We decided not to send questionnaires to parents of deceased children.

If in the questionnaire a (possible) hemangioma was reported, we asked parents or patients to send a photograph of the lesion. Following consent, medical charts were reviewed, or, when necessary, other institutions were asked for more detailed information about reported symptoms. The obtained data from the survey (age at diagnosis, location of a hemangioma, growth in time), photographs and medical chart reviews were analyzed anonymously. During a multidisciplinary meeting (two dermatologists, one plastic surgeon, one pediatric cardiologist and one pediatric hematologist, all members of the "Center of Congenital Vascular Anomalies Utrecht"; CAVU team) a diagnosis of hemangioma was confirmed or rejected. In addition it was discussed whether a subject met the criteria of PHACES syndrome in accordance with the criteria described by Metry et al (2009).

This study was judged as being not interventional by the ethics committee of the University Medical Center of Utrecht and thus did not require formal approval under Dutch law. All subjects provided informed consent for medical chart review and using information for research purposes.

Results

The database contained 286 children who were diagnosed with OAAP of which 90.9% had AC or an isolated hypoplastic aortic arch without intracardiac pathology. Twenty-six children (9.1%) had an IAA. Baseline patient characteristics are shown in table 1.

Table 1. Baseline characteristics of all patients

		All patients (n = 286) N (%)	Included patients (n = 164) N (%)	Deceased patients (n = 19) N (%)
Gender	Male	181 (63.3%)	108 (65.9%)	12 (63.2%)
Aortic arch obstruction	AC [a] Interruption	260 (90.9%) 26 (9.1%)	154 (93.9%) 10 (6.1%)	15 (79.0%) 4 (21.0%)
Complex disease [b]		164 (57.3%)	96 (58.5%)	17 (89.4%)
Aortic valve	Bicuspid Tricuspid (normal) Unknown	103 (36%) 171 (59.8%) 12 (4.2%)	67 (40.9%) 91 (55.5%) 6 (3.7%)	3 (15.8%) 10 (52.6%) 6 (31.6%)
Aberrant subclavian artery		10 (3.5%)	3 (1.8%)	5 (26.3%)

[a] Aortic Coarctation with or without hypoplasia of (segments) of the aortic arch or isolated hypoplastic aortic arch
[b] Complex disease is defined as coarctation in association with intracardiac pathology necessitating intervention[20]

As depicted in figure 1 (flowchart), 266 questionnaires were sent, with a response rate of 66% (n = 175). Because (parental) permission to use the data for research purposes was not obtained in 11 participants, 164 (62%) surveys were eventually analyzed. Baseline characteristics were comparable for the whole group (n=286) and only those who responded to the questionnaire (i.e. "included patients", n=164). In 23 cases (14%), patients or parents reported a possible IH. Eight of them were considered as true hemangiomas by the multidisciplinary team, based on patient history, photographs, chart review and, when available, histology reports.

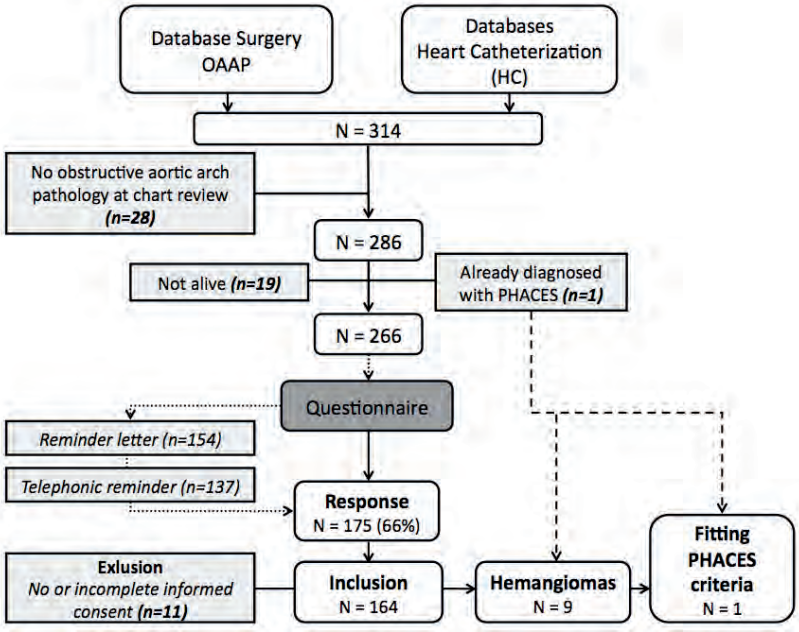

Fig. 1. Flowchart of inclusion

Characteristics of the 8 patients with a hemangioma (H01 – H08) are shown in table 2. No large (> 5cm in diameter) or segmental cervicofacial hemangiomas were diagnosed except for one patient (H09) who did not receive a questionnaire. This child was already known with PHACES syndrome, having a segmental hemangioma located mainly left sided in the periorbital and temporal region, with bilateral lesions retroauricular and a lesion of the soft palate. She had an atypical obstructed aortic arch (type C interruption) with agenesis of the left common carotid artery. During surgery a remarkable macroscopic aspect was noticed with perivascular scarring resembling like inflammatory alterations. When PHACES syndrome was suspected, further angiographic evaluation revealed hypoplasia of the left internal carotid and posterior communicating artery (major criteria) without symptoms of ischemia. In addition, the child had a sternal pit, which is also a major criterion.

Seven other hemangioma patients had classical AC (discrete narrowing distal to the left subclavian artery (LSA)), with or without BAV (bicuspid aortic valve), not matching with the specific aortic arch anomalies in PHACES syndrome. One patient (H05) revealed a slightly atypical hypoplasia of the transverse arch with a hypoplastic origin of the LSA without other remarkable aortic arch pathology. A large or segmental hemangioma of the face, necessary for the diagnosis of PHACES syndrome, was not present in this child. No neurological or other symptoms leading to the suspicion of PHACES syndrome were reported in any of the eight participants.

Of 286 patients with obstructive aortic arch disease, 19 patients deceased. Details of these children are summarized in table 3. None of the children had a hemangioma mentioned in their medical records or correspondence (including autopsy reports). Most children (9/19; 47%) had typical coarctation located distally of the LSA or did not have unusual characteristics of the coarctation mentioned (4/19; 21%). Two children (D10 and D15) had a coarctation proximal of the LSA and 4 children (D07, D11, D13, D14) had a type B interruption of the arch (between LCA and LSA), the most common type of IAA [20]. One child (D04) had a double aortic arch (minor criterion). None of the children had a right aortic arch. Ten patients (53%) died within the first 3 months of life, almost all due to circulatory failure as a consequence of their complex cardiac condition.

Table 2. Characteristics of hemangioma patients

Study nr.	Sex	Hemangioma [a]			Cardiovascular pathology			Other pathology	
		Location	Size (max) & type	Therapy	Aorta/aortic arch [c]	Aortic/mitral valve	Other cardiovascular	Neurologic involvement	Other
H01	M	Left upper torso	Oval spot, +/- 1 cm in diameter Focal	No	Juxtaductal AC with long segment narrowing (15 mm)	BAV	None	None (no imaging)	ADHD
H02	F	Right side of scalp	1 cm Focal plaque	No	Ridge/kinking and mild constriction of isthmus (>0.4 of AAo) Right aortic arch	Mild valvular and subvalvular aortic stenosis, functional BAV	Dextrocardia with atrial situs inversus, multiple VSDs; abnormal IVC, bilateral SVC	None (no imaging)	Polysplenia with functional asplenia (heterotaxy)
H03	F	Left upper arm	4 - 5 cm Focal plaque	No	AC DAo	BAV, parachute like mitral valve	VSD	None (ultrasound only)	No
H04	M	Left thumb	1 x 2 cm Focal	No	Juxtaductal AC with hypoplastic transverse arch	BAV	VSD, PFO, LVH, subaortic stenosis	None (no imaging)	Inguinal hernia
H05	M	Right scapula	3 cm Focal	No	Hypoplastic transverse arch between LCA and arterial ligament (15 mm segment) with slightly hypoplastic LSA origin	Normal	Mild peripheral LPA stenosis	None (no imaging)	Recurrent respiratory tract infections Mild laryngo-malacy
H06	M	Left lower back	3 - 4 mm Focal nodule	No	Severe AC with hypoplastic transverse arch	Stenotic BAV; parachute mitral valve with stenosis (Shone variant)	PFO, Mild subvalvular aortic obstruction (abortive Shone complex), Left SVC	None (ultrasound only)	No
H07	F	Left flank	1 x 0.5cm Focal	Surgical excision (PA: diagnosis confirmed)	AC DAo with hypoplastic transverse arch	Normal	VSD	None (no imaging)	ADHD
H08	M	Left thigh and toe (side unknown)	Thigh: 2 cm Toe: pinpoint, subcutaneous	No	AC DAo	BAV	PFO	None (no imaging)	No
H09	F	Face, mainly left side [b] Soft palate	Segmental / multifocal	Atenolol	IAA type C with (secundary) atresia left CCA	Normal	Bilateral SVC	Hypoplasia of left ICA and PCA Normal neurologic development at age 2 yrs	Sternal scar Genetics: Duplication 12q24.21

[a] In most cases determined by parental information in the absence of medical reportage

[b] Left temporal and periorbital, left auriculair helix. Bilateral retroauricular

[c] Hypoplastic aortic arch defined as diameter of isthmus < 40% of AAo, proximal transverse arch < 60% of AAo or distal transverse arch < 50% of AAo [34]. The term 'small' is used when no diameters were available or when not meeting the definition of hypoplasia.

ABBREVIATIONS: **AAo** Ascending Aorta; **AAR** Aortic Arch Reconstruction; **AC** Aortic Coarctation; **ADHD** Attention Deficit Disorder with Hyperactivity; **BAV** Bicuspid Aortic Valve; **CCA** Common Carotid Artery; **DAo** Descending Aorta; **EEA** End-to-End Anastomosis; **IAA** Interrupted Aortic Arch; **ICA** Internal Carotid Artery; **IVC** Inferior Vena Cava; **LPA** Left Pulmonary Artery; **LSA** Left Subclavian Artery; **LVH** Left Ventricle Hypertrophy; **PA** Pathology; **PCA** Posterior Communicating Artery; **PFO** Persistant Foramen Ovale; **SVC** Superior Vena Cava; **VSD** Ventricular Septal Defect

Table 3. Characteristics of deceased patients

Study Nr.	Sex	Cardiovascular pathology			Other pathology	Death		IH	Comments
		Aorta/aortic arch [a]	Left Valves	Other cardiovascular		Age of death	Cause of death	In medical record	
D01	M	HLHS	Unknown	LPA stenosis	Factor VII deficiency	12 years	Circulatory insufficiency / cardiac (presumably secondary to sepsis, embolisms, myocarditis, coronary ischemia)	No	
D02	M	Juxtaductal AC with small transverse arch	Normal	TGA, VSD, ASD, DORV, coronary anomaly	Hemorrhage adrenal gland, testicular hydrocele	2 months	Circulatory insufficiency / cardiac	No	
D03	F	AC Dao wit small transverse arch	Small mitral valve	ASD I, PDA	Multiple dysmorphic features (incl. down slanted eyes, low set ears, long fingers, four finger line)	4 months	Pneumonia	No	Genetics: triploidy chromosome 15 (unbalanced translocation chr. 4 – 15)
D04	F	Juxtaductal AC Double aortic arch	Normal	PFO	Prematurity (33 weeks) Bilateral subependymal hemorrhage	Unknown (> 7 months)	Unknown	No	Pathology report: ductal tissue in whole AC segment, no fibrosis or necrosis as seen in PHACES vasculopathy {Chad 2012; Bayer in press}
D05	M	AC	Normal	ccTGA, VSD, DORV, PA aneurysm and stenosis, PH	Recurrent atelectase, hypermobility, palatoschisis with facial dysmorphism (suspicion of Pierre Robin sequence)	10 years	Perioperative cardiac failure	No	Genetically excluded Marfan or Ehler Danlos disease
D06	M	Juxtaductal AC Overriding aorta	Dysplasia of mitral valve	VSD, ASD II, partial APVR	Bilateral choroideal coloboma, webbed neck, cysts in plexus choroidius, mega-cisterna magna, vermal hypoplasia (Dandy Walker variant), bronchial malacy, hepatosplenomegaly, biliary anomaly	4 ½ months	PH and bronchopneumonia	No (autopsy report)	Genetics: suspicion of cerebellar-craniofacial-cardiac (3C) or Joubert's syndrome
D07	F	IAA type B	Normal	Malalignment VSD, subaortic stenosis	None	4 days	During cardiac surgery (hemorrhage and myocardial infarction)	No	
D08	F	Juxtaductal AC Aberrant RSA	Normal	AVSD	Trisomy 21	6 months	Unknown (most likely due to pneumonia)	No dermatologic abnormalities	

Table 3. Characteristics of deceased patients *(continued)*

Study Nr.	Sex	Cardiovascular pathology			Other pathology	Death		IH	Comments
		Aorta/aortic arch [a]	Left Valves	Other cardiovascular		Age of death	Cause of death	In medical record	
D10	M	AC proximal of origin LSA	Cleft mitral valve	HLHS (forme fruste), AVSD	Bilateral cheilognathoschisis, testicular hydrocele, hemiparesis due to cerebral infarct [b] (large medial cerebral artery right infarct with hemorrhagic component)	3 months	Untreatable cardiac condition	No	No MRA brain imaging
D11	M	IAA type B Aberrant origin of the RSA	BAV	VSD, subaortic stenosis	Prematurity (35 weeks), inguinal hernia with testicular hydrocele, small airway disease	2 ¼ years	Unknown (most likely cardiac failure due to chordal rupture of mitral valve)	No	
D12	M	HLHS	Stenotic BAV	(prenatally?) Closed foramen ovale	Prematurity (31 + 5/7 weeks), ischemic cerebral lesions, potentially prenatally developed secondary to congenital heart disease	4 days	Severe and untreatable cardiac condition	No (autopsy report)	No abnormalities found during brain autopsy except for old and recent hypoxic lesions in cerebrum
D13	M	IAA type B Arteria lusoria	Doming and thickening of aortic valve	VSD, subaortic stenosis, DORV	Tracheomalacy, horseshoe kidney with hydronephrosis, costovertebral anomalies, multiple dysmorphic features (retro/micrognathia, long fingers, sandal gap, hypospadia)	6 months	Unknown (during hospitalization after cardiac procedures)	No	Genetics: suspicion of osteo-vertebral chondrodysplasia
D14	M	IAA type B Arteria lusoria	BAV	VSD, ASD, LVOTO, PA stenosis, PDA,	22q11 deletion syndrome, recurrent SVC syndrome/ thrombotic events, cerebral (periventricular) hemorrhage (most likely due to venous infarction), urethral stricture, developmental delay, auto-immune enteropathy	1 year and 8 months	Pulmonary detoriation, cutaneousGVHD and suspicion of pulmonary fungal infection after stem cell transplantation	No derma-tologic abnorma-lities	

Table 3. Characteristics of deceased patients *(continued)*

Study Nr.	Sex	Cardiovascular pathology			Other pathology	Death		IH	Comments
		Aorta/aortic arch [a]	Left Valves	Other cardiovascular		Age of death	Cause of death	In medical record	
D15	M	HLHS Arteria lusoria	Small aortic and mitral valve	ASD, left SVC, PDA	Hypoplasia of pons and vermis, partial agenesis of corpus callosum, unilateral hydronephrosis, dysplastic kidney with cyst, Pierre Robin sequence, bilateral conductive hearing loss, multiple skeletal deformities (scoliosis, abnormal rib position, abnormal ossification pubic bone, rockerbottom feet, digital abnormalities), multiple other dysmorphic features (inguinal hernia, tracheomalacy)	2 months	Severe respiratory obstructive incident	No	
D16	M	AC with hypoplastic transverse arch	Normal	VSD	Necrotizing enterocolitis	2 months	Bowel perforation secondary to necrotizing enterocolitis	No	
D17	F	HLHS	Mitral valve hypoplasia	Dextro/mesocardia, VSD, ASD, partial APVR (Scimitar syndrome), hypoplasia RPA, left SVC, MAPCAs	Hypoplasia right lung with lung sequestering (Scimitar syndrome), PH	5 weeks	Circulatory and respiratory failure due to progressive PH	No	
D18	F	AC distal of LSA with small transverse arch	Normal	Mesocardia, VSD, ASD, complete APVR (Scimitar syndrome), agenesis LPA, hypoplasia RPA, MAPCA, PDA	Omphalocele, PH, hypoplasia right lung with lung sequestering (Scimitar syndrome), male chromosomal pattern (XY) with female phenotype	7 days	Untreatable cardiac condition	No	
D19	F	AC DAo with small arch	Small aortic valve	TGA, VSD, OFO, DORV	Necrotizing enterocolitis, multiple ischemic cerebral lesions on MRI [b]	2 months	Progressive circulatory insufficiency	No	

[a] Hypoplastic aortic arch defined as diameter of isthmus < 40% of AAo, proximal transverse arch < 60% of AAo or distal transverse arch < 50% of AAo [34]. The term 'small' is used when no diameters were available or when not meeting the definition of ypoplasia.
[b] Considered to be consequence of cardiovascular condition and/or surgical procedure

ABBREVIATIONS: **AAo** Ascending Aorta; **AAR** Aortic Arch Reconstruction; **AC** Aortic Coarctation; **APVR** Anomalous Pulmonary Venous Return; **ASD** Atrial Septal Defect; **AVSD** Atrioventricular Septal Defect; **BAV** Bicuspid Aortic Valve; **DAo** Descending Aorta; **DORV** Double Outlet Right Ventricle; **EEA** End-to-End Anastomosis; **GVHD** Graft-Versus-Host-Disease; **HLHS** Hypoplastic Left Heart Syndrome; **IAA** Interrupted Aortic Arch; **IVC** Inferior Vena Cava; **LPA** Left Pulmonary Artery; **LSA** Left Subclavian Artery; **LVOTO** Left Ventricular Outlet Tract Obstruction; **MAPCA** Major Aortopulmonary Collateral artery; **PDA** Persistent Ductus Arteriosus; **PFO** Persistant Foramen Ovale; **PH** Pulmonary Hypertension; **RPA** Right Pulmonary Artery; **RSA** Right Subclavian Artery; **SVC** Superior Vena Cava; **(cc)TGA** (congenital corrected) Transposition of Great Arteries; **VA** Vertebral Artery; **VSD** Ventricular Septal Defect

Discussion

AC is a relatively common congenital abnormality. Within the PHACES spectrum, AC and IAA account for 45% of the cardiovascular anomalies as mentioned by Bayer et al (2013). As IH, the hallmark of PHACES syndrome, is highly prevalent in the healthy population, the appearance of IH in our study population of OAAP patients could also be by normal distribution. This study demonstrates that PHACES syndrome is uncommon in patients with OAAP.

IH and PHACES prevalence

A recent prospective study among the Dutch population by Hoornweg et al (2012), showed an IH prevalence of 9.9% in newborns (0 – 16 months of age). The relatively low prevalence we found (5.5%) is most likely due to recall bias, lack of registration in medical records by physicians of these benign lesions or misdiagnoses because of the retrospective nature of assessment.

In contrast, the actual prevalence of PHACES syndrome is unknown. A frequency of 2.3% in children with IH was reported by Metry, et al (2006). In the same study, PHACES was diagnosed in 20% of IH patients with the segmental facial type (approximately 10% of all IH), which is a characteristic feature and main criterion for definite diagnosis of PHACES. Given an IH prevalence of 9.9% in the Dutch population, the prevalence of PHACES is suggested to be as high as 1:500 children. One fifth of all PHACES patients are affected by AC or IAA [10], suggesting that approximately 1 per 2500 children has PHACES with aortic arch obstruction. As the birth prevalence of AC is also around 1:2000-3000 (Van der Linde et al 2011, EUROCAT Central Registry and Website Database 2013), this would suggest that a large proportion of, if not all, AC patients could be diagnosed with PHACES.

We only found one AC patient (0.6%) with an already diagnosed PHACES syndrome in the studied cohort. This is substantially less than expected as suggested by Metry et al (2006). It should be recognized though that the cohort studied by Metry et al (2006) only concerned IH patients in tertiary dermatology centers, which may have caused selection bias that resulted in the observed high prevalence of PHACES in IH patients.

The prevalence we found here is also lower than reported by Prada et al (2010) in which 4 cervicofacial hemangiomas were shown with segmental distribution or ulceration in a cohort of 63 subjects (6.3%). We diagnosed only one child with a similar hemangioma in our cohort (0.6%). There's no direct explanation for this remarkable difference in prevalence, but it might be partially explained by Prada et al using an outdated broad definition of Frieden et al (1996). This inclusive case definition consists of facial hemangioma plus 1 or more extracutaneous features. In contrast, we used the current diagnostic criteria as

proposed by Metry et al (2009) in a consensus statement. This statement stratifies patients into 2 categories: [1] PHACES syndrome or [2] possible PHACES syndrome and uses major and minor criteria for the diagnosis.

A strong relationship between the occurrence of aortic arch obstruction and segmental IH, has been hypothesized by others (Metry et al 2009 and Bronzetti et al 2004). Despite the fact that our single PHACES case accounts for 11% of the identified hemangiomas in AC patients, which is much higher than the 2.3% of 'general' IH patients as reported by Metry et al (2006), our limited cohort size makes it difficult to draw definite conclusions.

Diagnostic considerations

Except for the child with already diagnosed PHACES syndrome (H09), no patients fitted the diagnostic criteria for "definite" diagnosis of PHACES based on the hemangioma characteristics.

However, two patients with IH (H01 and H05) may be diagnosed with "possible" PHACES for having a hemangioma on the upper torso, as stated in the diagnostic criteria by Metry et al (2009). The possibility of PHACES syndrome in children with nonfacial hemangiomas is based on case reports of children with large segmental hemangiomas of the upper trunk or arm with or without minor facial involvement (Metry et al 2006 and Nabatian et al 2011). Our two 'possible PHACES' cases however exhibited a small (< 5 cm in diameter), non-segmental hemangioma and thus were not suspected for PHACES syndrome by our CAVU expert team. The data suggest that occurrence of IH in this cohort (except for H09) seems to be coincidental rather than related with OAAP.

The aortic abnormalities found in PHACES patients represent a distinctive morphologic entity with unusually complex and unpredictable anatomic involvement. Whereas the "classical" coarctation involves a discrete part of the proximal descending (juxtaductal) segment of the aorta, the coarctation observed in PHACES syndrome has been described to consist of a long-segment narrowing of the transverse arch with unusual dilation and aneurysm formation of adjacent arch segments (Metry et al 2006, Metry et al 2001, Rao et al 2008, Bronzetti et al 2004). These arch anomalies are often associated with abnormalities of the brachiocephalic vessels (dilation, tortuosity, and aberrant subclavian artery origin) and aortic arch sidedness as written by Metry et al (2009) and Bronzetti et al (2004).

The prevalence of BAV is as high as 50-80% in the "classic" coarctation. In PHACES syndrome however no aortic or mitral valve pathology is seen in PHACES syndrome (Metry et al 2009 and Beekman et al 2008). A recent study of 150 PHACES cases by Bayer et al (2013), showed that left heart valve pathology (BAV in particular) was completely absent in all of the 28 coarctation patients.

Our child with PHACES syndrome revealed such unusual anatomy (interruption between innominate and left common carotid artery with absence of the left carotid artery). No unusual dilation, aneurysm formation or abnormalities of the brachiocephalic vessels, in particular aberrant origin of the right subclavian artery, were observed in the other IH patients. Despite the slightly atypical aortic arch (long segment hypoplasia of arch and hypoplastic origin of LSA) in H05, this child was not considered to have PHACES. In addition, the aortic arch in the other "possible" PHACES subject (H01) did neither correspond with the bizarre arch anatomy seen in PHACES syndrome.

Deceased patients

Another explanation for the low PHACES prevalence in our study might be that potential PHACES patients died early in life due to complications of cardio- or cerebrovascular anomalies. Therefore, we investigated the available data of deceased OAAP patients.

No hemangiomas were mentioned in medical records or autopsy reports of these children.

The diagnosis of PHACES could be deliberated in some deceased children based on certain aortic arch anomalies (e.g. double aortic arch or aberrant subclavian artery), neurologic sequelae or dysmorphic features (such as micrognathia or schizis). For all these there were arguments against this diagnosis, for example the presence of (cardiac) abnormalities which are unknown in PHACES, being diagnosed with or being suspected for another syndrome (e.g. 22q11 deletion syndrome). Unfortunately, no definite answers can be given due to lack of angiographic imaging, missing data and unreliable documentation of possible hemangiomas.

Conclusion

In this retrospective cohort of 164 OAAP patients, one child met the PHACES criteria, indicating that PHACES syndrome is rare in OAAP patients. Due to limited cohort size this study was underpowered to provide final proof of an association between IH and obstructive aortic arch pathology.

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Chapter 8

Deep congenital hemangioma: Prenatal diagnosis and follow-up

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Abstract

Congenital hemangiomas (CH) are rare benign vascular tumors that are present at birth after full development *in utero*. With increasing importance of prenatal screening and improved imaging techniques, vascular tumors will be detected more frequently during examination. Ultrasonographers and obstetricians should be aware of these vascular tumors, their differential diagnosis and prognosis. Not only caregivers need optimal counseling, but also the professionals involved should have knowledge about these anomalies, because of an increased risk of complications during and after delivery of the child. Here we present a child with a CH of the leg and discuss prenatal diagnosis, intra-partum management, and postnatal follow up.

Case Reports in Perinatal Medicine. 2012; 1(1-2): 55–8

Case presentation

A 30-year-old woman, G2P1 with a spontaneous bichorionic twin pregnancy, was referred to our hospital at 29 weeks of gestation, after routine sonography had revealed a superficial growing mass on the leg of one of the fetuses, suggestive of a hemangioma. The mother's medical history and the antenatal course of her current pregnancy were unremarkable.

At 23^{+1} weeks of gestation, ultrasound (US) examination showed a homogeneous soft tissue mass (approximately 2.7x0.8cm) of the right lower leg in one of the fetuses, with multiple feeding arteries and drained by the popliteal vein, suggestive of a hemangioma (fig. 1A and 1B). US examination at 29^{+6} weeks of gestation showed moderate insufficiency of the tricuspid valve and Doppler examination revealed increased flow in the umbilical vein with a normal pulsatility index of the ductus venosus. Biometry of both fetuses was appropriate for gestational age. During follow up, the mass increased to a size of 1.5x5.0x4.0cm at 32^{+6} weeks of gestation (fig. 1C and 1D). Despite previous signs of hyperdynamic circulation, the child did not develop cardiac decompensation and circulation parameters turned normal. At that time, on basis of these findings the lesion was suspected to be a congenital hemangioma (CH). The parents were informed about the possible diagnoses and the benign course of these lesions. Close antenatal follow up was advised using US to score the size and the development of the lesion. The professionals involved were informed about the risks during and after delivery and a caesarian section (CS) was advised.

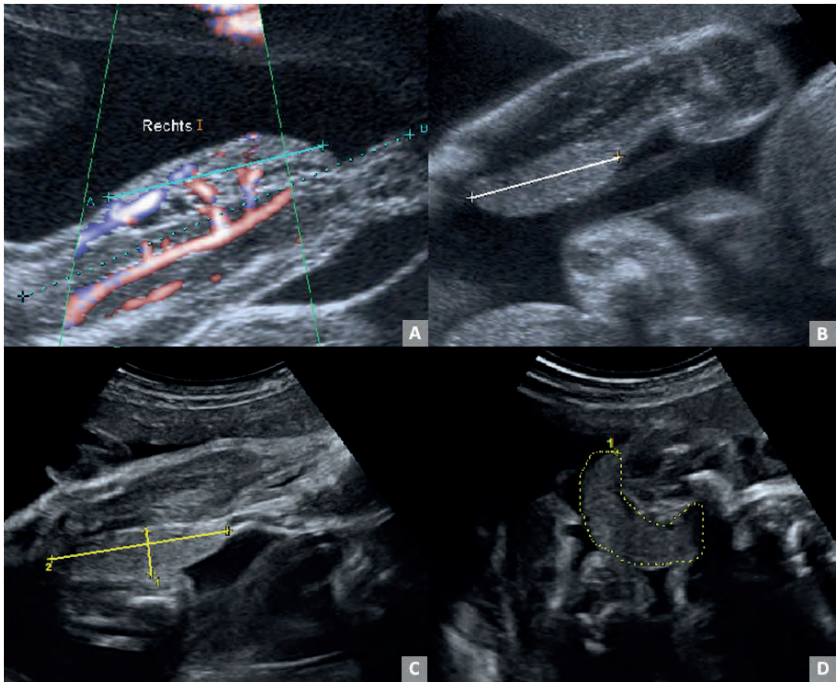

Figure 1. US images
(A) First ultrasound at 23^{+1} weeks of gestational age showing a mass on the mediodorsal side of the right lower leg, approx. 2,7 cm in length (cyan line). Doppler imaging shows extended vascularity of the lesion with afferent and efferent vessels.
(B) On US at 28^{+6} weeks of gestation, the well-defined homogeneous soft tissue mass has extended to a length of 3,9 cm (white line).
(C) Ultrasound examination at 32^{+6} weeks of gestation showing an increasing size of approx. 1.5 x 5 cm (yellow lines).
(D) On the same ultrasound, incomplete circumferential growth of the tumor is visible (circumference 11,3 cm, yellow dotted line).

At 35^{+1} weeks of gestation, the mother presented with spontaneous labor and a planned CS was performed. The first child was delivered without complications, seemed healthy at first physical exam and was admitted because of prematurity. Then, the affected boy, weighing 2740g, was delivered. Because of persistent respiratory distress, the infant had to be transferred to the neonatal intensive care unit, where continuous positive airway pressure (CPAP) was started. Respiratory distress was thought to be the result of wet lung disease and resolved within 2 days following CPAP. No signs of cardiac decompensation were observed. Further neonatal physical examination was completely normal besides the known tumor of the right leg and the respiratory symptoms.

An elastic purple blue tumor with a pale edge and a dark purple spot was seen on the

medial side of the right distal leg, approximately 5cm in length (fig. 2A). Postnatal US showed a well-defined inhomogeneous lesion with extended vascularization measuring 4.4x5.5x0.6cm. The lesion appeared to be subcutaneous without involvement of underlying structures. Magnetic resonance imaging (MRI) corresponded with the suggested diagnosis of CH; the hypo-intense signal on T1-weighted and hyper-intensity on T2-weighted MRI scan, in combination with the presence of normal superficial veins in the subcutaneous lesion, supported the presumed benign character of the lesion. Outpatient follow-up showed impressive blanching and involution of the tumor within 6 months (fig. 2B), which confirmed the diagnosis of rapidly involuting CH.

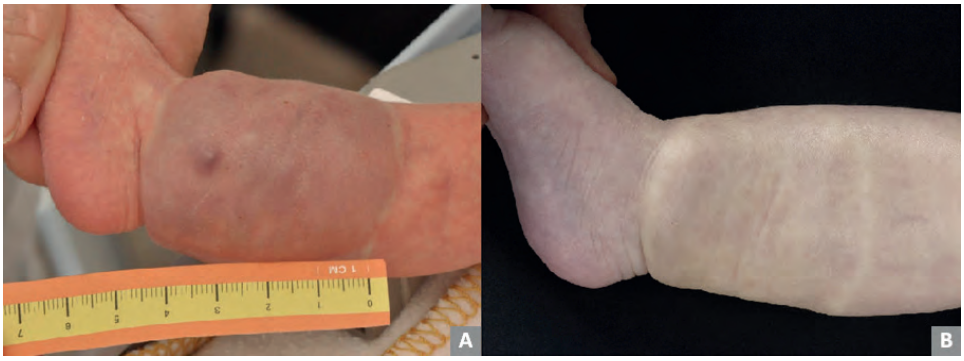

Figure 2. Photographs
(A) Cutaneous hemangioma of the right lower leg with the length of approx. 5 cm.
(B) Outpatient follow up shows impressive discoloration and shrinking of the hemangioma 6 months after birth.

Discussion

CHs are benign vascular tumors that reach maturity *in utero* characteristically with no further growth after birth. There are two types of CH: non-involuting congenital hemangiomas (NICH) and rapidly involuting congenital hemangiomas (RICH). NICHs do not regress, whereas RICHs show complete spontaneous regression within 12 to 24 months in most cases.[1] Therefore, RICH does not require treatment initially and observation is justified.[1,2] However, occurrence of complications, such as affecting vital organs or ulceration may necessitate intervention.[3] Although positive results have been reported, it is unclear whether new therapies for infantile hemangioma (IH) such as a beta-blocker are effective in treating CH.[2,3,4,5]

When detecting a well-vascularized, deep tumor *in utero*, other vascular tumors, such as kaposiform hemangioendothelioma and tufted angioma, also have to be considered because these latter lesions could be associated with Kasabach-Merritt Syndrome (KMS). This rare consumption thrombocytopenia carries a significant risk of perinatal complications, including death. However, this phenomenon is not seen in CH or IH.[2] Hemangiomas typically exhibit a homogeneous, hypo-echoic signal, intense diffuse vascularity and high flow on US-Doppler which is not typical for other vascular tumors.[4,5,6,7] High flow is also typical for (combined) arterial malformations (AMs) and IHs though, which can be differentiated by MRI. Cystic lesions are more suggestive for lymphatic malformations, whereas calcifications are suggestive for venous malformations[8]. Both findings can also be found in teratomas.[9] When distinguishing possible diagnoses before birth has serious consequences for planning perinatal care or when uncertainty about diagnosis (e.g. CH or AM) or prognosis of the lesion remains after enhanced Doppler US, fetal MRI is indicated.[8,9]

Close antenatal evaluation includes frequent US to monitor the lesion size and blood flow. Large hemangiomas are associated with congestive heart failure due to a hyperdynamic circulation leading to increased cardiac output, therefore fetal circulatory parameters should also be monitored.[2,3,10] Termination of pregnancy has been considered in published cases in which the lesion was interfering with vital functions.[10] Regarding delivery, an elective CS is often recommended in the literature because of the possibility of fetal thrombocytopenia due to KMS with an increased chance of bleeding during normal or instrumental vaginal delivery.[2] Because of the higher *a priori* chance of an emergency CS or intrapartum fetal manipulation with the risk of trauma to the hemangioma in this twin pregnancy, we also performed a CS.

After birth, follow up with a multidisciplinary approach including frequent observation of the tumor will confirm the prenatal and postnatal diagnosis. Especially involution postnatally excludes malignant tumors and differentiates RICH from NICH. A biopsy can further distinguish or confirm diagnoses based on typical histopathological characteristics. A GLUT-1 staining for example, can differentiate an IF from a RICH and other vascular tumors.[4,6] However, diagnosis can often be made on clinical ground and ultrasound alone.[6,8]

In conclusion, we reported a case of a prenatally diagnosed deep hemangioma of the right lower leg in twin pregnancy. During close follow-up after birth, it appeared to be a RICH, justifying the conservative approach. When confronted with a vascular lesion, ultrasonographers and obstetricians should be aware of the differential diagnosis. Caregivers of the child and the involved professionals should be adequately informed by a multidisciplinary team of experts, which will closely monitor the vascular tumor pre-, peri- and postnatally.

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Chapter 9

Evaluation of the therapeutic guideline for kaposiform hemangioendothelioma in Dutch case series and review of the literature

Martine F Raphael, Nathalie Krukziener, Suzanne GMA Pasmans, Peter CJ de Laat

Abstract

Purpose
Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor. It may lead to increased morbidity and mortality especially when the coagulopathy, Kasabach Merritt phenomenon (KMP), is present. In 2013 a consensus derived practice standards plan was published for this patient population. The purpose of this study was to evaluate the treatment strategies in a Dutch KHE cohort and to review the literature for treatment options in KHE cases compared to the aforementioned treatment plan.

Methods
We systematically reviewed the literature from 1994-2016 on therapeutic options for KHE in children and retrospectively reviewed the data of 34 patients with KHE in the Netherlands over the last two decades.

Results
A total of 92 studies with 350 patients met all inclusion criteria. KMP was present in 291 KHE cases in 79 studies. Treatment regimens could be categorized in four groups; no therapy, surgery, local interventions and systemic therapy. Following the publication of the consensus derived practice standards plan in 2013, no reports could be identified in which patients without KMP were treated with oral prednisolone monotherapy. The first line therapy from the consensus guideline for KHE patients with KMP, a combination of corticosteroids and vincristine, was used in 14 studies since 2013.

Abstract *(continued)*

The medical records of 34 Dutch KHE patients were evaluated. The median age of initial presentation was two months (range, birth to 32 months). Four patients had lesions, which were already visible on prenatal ultrasonography and those were diagnosed after birth as KHE. Twenty-four patients had progressive enlargement of the tumor as a presenting symptom (71%). Twenty-six patients (76%) showed symptoms of coagulopathy (bruising, petechiae, bleeding). KHE most frequently involved the liver (n=13; 38%), followed by the extremities (n=10; 29%), cervicofacial (n=6; 18%) and the torso (n=5; 15%). Prednisolone was preferred as systemic treatment (n=25 patients; 96%), but in 21 cases (81%), at least a combination of prednisolone and vincristine was used as initial treatment. Since 2013 all Dutch KHE patients were treated according to the consensus derived practice standards plan.

Conclusion
Adherence to the consensus derived practice standards plan has not been studied so far. We show that most cases reported after 2013 did not follow the recommendations of the practice standards plan. International collaboration using a registry should be undertaken to validate and revise the consensus derived practice standards plan for patients with KHE with and without KMP and for patients with vascular lesions in the liver.

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Introduction

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor that mainly affects children. In the International Society for the Study of Vascular Anomalies (ISSVA) classification it is known as a locally aggressive or borderline vascular tumor (1). KHE most often presents as a solitary, firm lesion with ill-defined margins located in the skin or soft tissue. KHE typically occurs on the lateral neck, extremities and torso. Clinical presentation is variable, with a wide range of symptoms and complications. A biopsy is not commonly performed in KHE because of risk of haemorrhage. Therefore the histological diagnosis is more often obtained after surgery. Magnetic resonance imaging (MRI) is the modality of choice to diagnose KHE. KHEs decrease spontaneously in size with time, although complete regression is uncommon (2).

KHE is often associated with a coagulopathy known as Kasabach-Merritt phenomenon (KMP). It is a rare clinical and laboratory entity consisting of profound thrombocytopenia, hypofibrinogenemia, consumptive coagulopathy and elevated d-dimers. Intralesional platelet trapping within the microvasculature has been suggested to cause KMP (3). Subsequent platelet consumption and activation of coagulation within the tumor results in a form of disseminated intravascular coagulation, with both the propensity of clotting and the risk of bleeding. After the resolution of the coagulopathy, residua of tumors associated with KMP are common (2). Clinically and histologically these remnant lesions differ from involuted infantile hemangiomas (2).

Aggressive treatment is necessary for symptomatic KHE, because expansive tumor growth and coagulopathy can be life threatening with a mortality rate up to 30% (4). Although complete surgical excision has been proposed as the gold standard, it is most often not a suitable option. Embolization is often used as an adjuvant therapy in the treatment of KHE, but its effects as single treatment option is not well established. Many pharmacological therapies with corticosteroids, vincristine, propranolol and/or sirolimus have been described, with various outcomes. In 2011 an effort was made to endorse a consensus derived practice standards plan (further referred as guideline). This uniform approach of care for this heterogenic disorder was finally published in 2013 (5). For patients with KHE without KMP oral prednisolone is the recommended first line therapy. The initial therapy for KHE with KMP was defined as a combination of systemic corticosteroids and vincristine. Surgical resection or embolization may be treatment of choice for KHE patients with a life-threatening tumor for whom the time of response to medical therapy is considered too long or may be secondary considerations for tumors that have failed medical treatment (5).

Given the challenging treatment considerations for KHE, this study was designed to systematically review the literature with therapeutic options used for KHE in children. Furthermore we retrospectively compared the therapy used in KHE patients in the Netherlands with the proposed treatment plan of the consensus meeting in 2011.

Methods

The medical records of KHE patients in all eight Dutch university medical centers from 1990 to 2016 were reviewed to define a cohort of patients with probable KHE. Data were collected using standardized case report forms that include age of onset, year of therapy, presenting signs/symptoms, anatomic location, platelet count, markers of coagulation, therapy and outcome. KMP was defined as platelet count of < 150x10E9/L and/or coagulation disorders. Histopathological confirmation was not required for diagnosis.

In January 2016, MEDLINE and EMBASE databases were searched systematically for the search terms ("Kaposiform Hemangioendothelioma"[Mesh Terms] OR "KHE"[all fields]) OR "Kaposiform Hemangioendothelioma"[all fields] AND ("therapy"[Mesh Terms] OR "therapy"[all fields] OR "treatment"[all fields] OR "treating"[all fields]) and applied data limitation starting from 1994-2016. Two reviewers (M.R. and N.K.) independently listed all included manuscripts, mainly case studies describing medical treatment for children ≤18 years with KHE. Studies were de-duplicated and excluded if only abstracts were available or if not written in English or Dutch. The following data were extracted from each article: number of cases, type of therapy, presence of KMP, treatment regimen and follow-up duration. The discrepancies between the reviewers were resolved by consensus.

Results

Literature

Initially 410 potential eligible studies were identified in the literature search (Figure 1). After excluding double reports 289 unique articles remained. A total of 83 studies met all inclusion criteria for this review while citation screening and other sources revealed another nine studies (n=92). In total 350 patients were described of whom 28 patients died (8%) (Table 1). In 26 studies more than one patient with KHE was reported (range 2-37 patients). KMP was described in 291 cases in a total of 79 studies. Follow-up duration up to 28 years was reported.

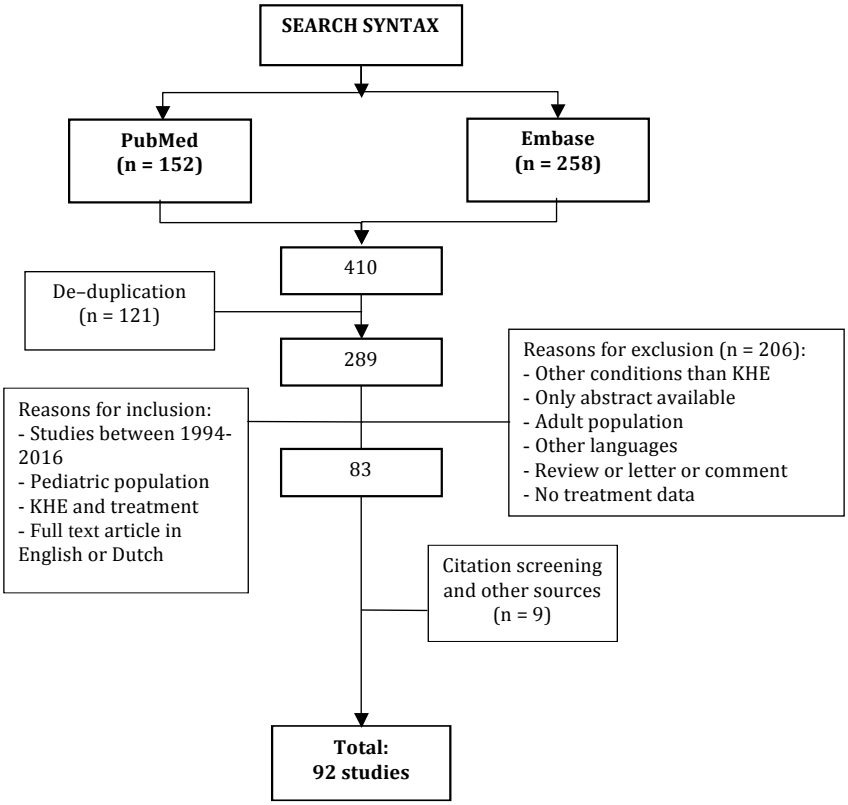

Fig. 1. Flow diagram search strategy
KHE= kaposiform hemangioendothelioma

KHE therapy in literature

Treatment regimens varied, but could be classified in four different groups; no therapy (n=5 studies), surgery (n=38 studies), local interventions (e.g. embolization, sclerotherapy, radiation therapy, MESH suture, compression therapy, ligation or local injection therapy) (n=28 studies) and systemic therapy (n=79 studies) (Table 1). Systemic therapy could further be specified: in 64 studies corticosteroids were given, in 46 studies vincristine was used, interferon in 38, sirolimus in 11 (of which one with everolimus) and propranolol in 11 studies. Combination therapy with corticosteroids and vincristine was reported in 39 studies.

Table 1. Summary review study details

Nr	Year	Author	Patients (n=350)	KMP + (n=291)	KMP – (n=53)	Therapy	Follow up
1.	2015	Liu Q	22	15	7	steroids / urea injection / surgery (8), steroids / interferon / surgery (1), steroids / adenosine triphosphate / surgery (1), urea injection / surgery (1+, 4-), steroids / gammaglobuline / surgery (2), steroids / surgery (1), steroid / urea injection / gammaglobulin / surgery (1-), steroids / gammaglobuline / vitamin k / surgery (1), surgery (2-)	8-26 months 1 died
2.	2015	Yuan SM	18 1 TA	19		vincristine (3), surgery / vincristine (8), ethanol (8)	NA 6 died
3.	2015	O' Rafferty C	1	1		dexamethasone / vincristine / aspirin / ticlopidine	6 years
4.	2015	Lackner H	2	2		vincristine / prednisone / cyclophosphamide / sirolimus (1), sirolimus (1)	> 6 months
5.	2015	Vivas-Colmenares GV	1	1		vincristine / aspirin / ticlopidine	12 months
6.	2015	Iacobas I	1	1		sirolimus	1 year
7.	2015	Wang Z	37	37		steroids / vincristine (29), steroids / vincristine / sirolimus (5), steroids / vincristine / interferon (3)	mean 3.5 years 0 died
8.	2015	Wang Z	1	1		propranolol / methylprednisolone / vincristine / sirolimus	12 months
9.	2015	Sasson M	1	1		surgery	1 year
10.	2015	Li K	2	2		surgery / cyclophosphamide / adriamycin / etoposide / methyl-prednisolone / vincristine (1), steroids / vincristine (1)	2 years (n=1)
11.	2014	Kajiwara R	1	1		vincristine / propranolol	NA
12.	2014	Friedman AJ	1	1		steroids, vincristine	NA
13.	2014	Ergaz Z	1	1		none	patient died
14.	2014	Mardegan V	1	1		steroids	patient died
15.	2014	Nakaya T	1	1		prednisone	patient died
16.	2014	Shen W	7 1 TA	8		prednisone / ethanol injection (6) surgery / prednisone / ethanol injection (2)	12-36 months 0 died
17.	2014	Li K	3	3		propranolol / prednisone / mesh suture (2) propranolol / mesh suture (1)	6-12 months 0 died
18.	2014	Uno T	1	1		propranolol / prednisone / vincristine / everolimus	5 months
19.	2014	Choeyprasert W	1	1		propranolol	6 months

Table 1. Summary review study details *(continued)*

Nr	Year	Author	Patients (n=350)	KMP + (n=291)	KMP – (n=53)	Therapy	Follow up
20.	2014	Nakib G	1	1		prednisone / vincristine / sirolimus / cyclophosphamide / surgery / embolization	4 months
21.	2014	Kai L	6	6		steroids / vincristine / sirolimus (4) steroids / vincristine / cyclophosphamide / sirolimus (1) steroids / vincristine / interferon-alpha / sirolimus (1)	1-12 months 0 died
22.	2014	Malhotra Y	1	1		embolization / methylprednisolone / dexamethasone / propranolol / radiation therapy	33 months
23.	2014	Wallenstein MB	1	1		prednisolone / aminocaproic acid / vincristine / aspirin	18 months
24.	2013	Leung M	1	1		surgery	5 months
25.	2013	Oksiuta M	1	1		propranolol	2 years
26.	2013	Beaton A	1		1	none	6 months
27.	2013	Chan S	1	1		vincristine / sirolimus	NA
28.	2013	Downing A	1	1		methylprednisolone / prednisolone / vincristine	1 year
29.	2013	Goswamy J	1	1		prednisolone / embolization / vincristine	NA
30.	2013	Fernandez-Pineda I	8 3 TA	11		vincristine / aspirin / ticlopidine (2) prednisolone / vincristine / aspirin / ticlopidine (9) Interferon-alpha was used in half of the patients with no therapeutic effect	mean 4,5 yr (range 2-17 years) 0 died
31.	2013	Low IC	1		1	surgery	6 years
32.	2013	Yasui N	10 1 TA	11		prednisolone(1), prednisolone / interferon-alpha / chemotherapy (3), methylprednisolone / interferon-alpha / radiation therapy / chemotherapy(1), prednisolone / interferon-alpha / radiation therapy(1), prednisolone / propranolol(1), prednisolone / propranolol / interferon-alpha / chemotherapy(1), prednisolone / interferon-alpha / radiation therapy (1), prednisolone / chemotherapy(1), nafamostat mesilate(1) Chemotherapy is defined as vincristine, cyclophosphamide, carboplatin, actinomycin D, tetrahydropyranyladriamycin	max 16 months 1 died
33.	2013	Zhou S	1	1		prednisolone / dexamethasone / embolization	10 months
34.	2013	Funato M	1		1	steroids /Interleukin-2 / paclitaxel / doxorubicin / cisplatin	patient died
35.	2012	Chiu YE	9 2 TA	8	3	propranolol(2), propranolol / prednisolone / vincristine(3), propranolol / aspirin(1), propranolol / prednisolone(1), vincristine / methylprednisolone / prednisolone / propranolol / sirolimus(1) propranolol / embolization / prednisolone / vincristine(1), propranolol / prednisolone / aminocaprioc acid(1), propranolol / vincristine / cyclophosphamide / actinomycin D / prednisolone / interferon-alpha / radiation therapy / thalidomide / celecoxib / etoposide(1)	4-12 months

Table 1. Summary review study details *(continued)*

Nr	Year	Author	Patients (n=350)	KMP + (n=291)	KMP – (n=53)	Therapy	Follow up
36.	2012	Fuchimoto Y	1	1		prednisolone / radiation therapy / interferon-alpha / embolization / vincristine / actinomycin D / cyclophosphamide	6 years
37.	2012	Garcia - Monaco R	2	2		prednisolone / embolization / vincristine	6 months-3 years 0 died
38.	2012	Jiang RS	1	1		dexamethasone / prednisolone / methylprednisolone / beta-methasone / surgery	11 months
39.	2012	Barabash-Neila R	1	1		prednisone / vincristine / ticlopidine / aspirin	18 months
40.	2012	Thompson CV	1		1	surgery	32 months
41.	2011	Martin MC	1		1	surgery/steroids	14 months
42.	2011	del Pozo J	1	1		embolization / surgery / vincristine / interferon-alpha / aspirin / dypiridamol	3 years
43.	2011	Ma J.	2		2	surgery	5-15 years 0 died
44.	2011	Hermans DJ	1	1		propranolol / vincristine	2 months
45.	2011	Hammill AM	1	1		steroids / vincristine / cyclophosphamide / interferon-alpha / bevacizumab / embolization / sirolimus	NA
46.	2011	Zhu Y	1		1	none	3 years
47.	2011	Rekhi B	1	1		surgery / sclerotherapy	NA
48.	2010	Fernandez-Pineda I	1 1 TA	2		vincristine / aspirin / ticlopidine(1), prednisolone / vincristine / aspirin / ticlopidine(1)	NA 0 died
49.	2010	Blatt J	1	1		prednisolone / decadron / methylprednisolone / vincristine / embolization / sclerotherapy / propranolol / bevacizumab / recombinant factor VII / amicar / sirolimus	21 months
50.	2010	Indolfi P	1	1		vincristine / actinomycin D / surgery / interferon-alpha	8 years
51.	2010	Fahrtash F	3 KHE 3 TA 1 TA/KHE	3 KHE	4	vincristine (3 = 2 KHE & 1 TA), prednisolone / surgery / vincristine (1 TA KHE), interferon-alpha / vincristine (1 TA), prednisolone / vincristine (1 KHE), surgery / vincristine (1 TA)	4 months - 8 years 0 died
52.	2010	Terui K	1		1	surgery	3 years
53.	2010	Veening MA	1	1		vincristine / prednisone / interferon-alpha	NA
54.	2010	Alomari AK	1	1		corticosteroids / vincristine	6 years
55.	2010	Tamai N	1	1		prednisone	NA
56.	2009	Zahir ST	1	1		methylprednisolone / prednisolone / interferon-alpha / surgery	1 year

Table 1. Summary review study details *(continued)*

Nr	Year	Author	Patients (n=350)	KMP + (n=291)	KMP – (n=53)	Therapy	Follow up
57.	2009	Kwok K	1	1		surgery	3 months
58.	2009	López V	1	1		corticosteroids / interferon-alpha / vincristine / ticlopidine	1 year
59.	2009	O'Regan GM	3	3		methylprednisolone / prednisolone / interferon-alpha / vincristine / penthoxyphylline / embolization (1), prednisolone / embolization / vincristine / interferon-alpha / penthoxyphylline / tranexamic acid / ticlopidine / aspirin (1), methylprednisolone / vincristine / interferon-alpha	3-7 years 1 died
60.	2009	Hartman KR	1	1		surgery / methyl-prednisolone / aminocaproic acid / vincristine / interferon-alpha	48 months
61.	2009	Mukerji SS	1	1		dexamethasone / cyclophosphamide / vincristine	patient died
62.	2009	Rodriguez V	5 1 TA	6		methylprednisolone / vincristine (1), prednisolone / interferon-alpha (1), corticosteroids / radiation therapy / surgery (1), prednisolone (1), prednisolone / interferon-alpha (1), radiation(1)	3 months-28 years, 1 lost to follow up
63.	2009	Lisle JS	1		1	thalidomide / celecoxib	8 months
64.	2009	Leong E	2	2		prednisolone / methylprednisolone / interferon-alpha / radiotherapy(1), methylprednisolone / interferon-alpha / radiation therapy / surgery(1)	5-8 years 0 died
65.	2009	Cho WS	1		1	surgery / interferon-alpha / prednisolone	Patient died
66.	2008	Walsh MA	1	1		surgery / vincristine / prednisolone	NA
67.	2008	San Miguel FL	1	1		corticosteroids / surgery	1 month
68.	2008	Abass K	1	1		corticosteroids / vincristine / surgery	6 months
69.	2007	Kwok Williams M	1	1		prednisolone / surgery / interferon-alpha / radiation therapy	4.7 years
70.	2007	Hauer J	1	1		prednisolone / interferon-alpha / vincristine / cyclophosphamide / actinomycin D / methotrexate	NA
71.	2006	Harper L	1	1		interferon-alpha	3 years
72.	2006	Iwami D	1	1		corticosteroids / interferon-alpha	6 years
73.	2006	Deraedt K	1	1		surgery	NA
74.	2006	Chen RL	1	1		prednisolone / surgery / methylprednisolone / interferon-alpha / cyclophosphamide / vincristine	6 months
75.	2006	Wang SR	1	1		interferon-alpha / corticosteroids / radiation therapy / betamethason intralesional	Still therapy
76.	2005	DeFatta RJ	1		1	surgery	1 year
77.	2005	Gruman A	10		10	observation (5), interferon-alpha / prednisone / vincristine / surgery (1), corticosteroids (1), corticosteroids / vincristine (2), vincristine (1)	15 months - 7 years 0 died

Table 1. Summary review study details *(continued)*

Nr	Year	Author	Patients (n=350)	KMP + (n=291)	KMP – (n=53)	Therapy	
78.	2004	Lyons LL	31	14	11 *[6?]*	surgery (10), NA (11), steroids (2), interferon-alpha (2), surgery / radiation therapy (1), steroids / interferon-alpha (2), surgery / interferon-alpha (1), surgery / steroids(1), steroids / chemotherapy(1)	8 months - 15 years 4 Died
79.	2003	Chung MT	1	1		methylprednisone / interferon-alpha	14 months
80.	2003	Verhallen JTCM	1	1		prednisone / interferon-alpha / vincristine	NA
81.	2002	Walker GM	1	1		methylprednisolone / interferon-alpha / embolization / sclerosis with absolute alcohol / surgery	6 months
82.	2002	Haisley-Royster C	15	15		vincristine / interferon-alpha / corticosteroids / embolization (1), corticosteroids / vincristine (7), amicar / corticosteroids / interferon-alpha (1), corticosteroids / ticlopidine / aspirin / vincristine (1), ticlopidine / aspirin / vincristine (1), corticosteroids / interferon-alpha / embolization / vincristine (1), corticosteroids / ticlopidine / aspirin / interferon-alpha / vincristine (1) interferon-alpha / amicar / vincristine (1), corticosteroids / radiation therapy / vincristine (1)	1-32 months
83.	2001	Mac-Moune Lai F	3	2	1	surgery / interferon-alpha	>8 years
84.	2000	Shin HY	37	37		surgery (2), steroids / radiation therapy (28), interferon-alpha / steroids (5)	Median 6 years and 3 months 2 died
85.	1998	Arnaout M.K.	1	1		methylprednisolone	NA
86.	1998	Hu B	1	1		surgery / corticosteroids / cyclophosphamide / vincristine / actinomycin D	3 months
87.	1998	Blei F	1	1		embolization / interferon-alpha / cyclophosphamide / epsilon aminocaproic acid / compression therapy	NA
88.	1998	Beaubien ER	1		1	prednisone	Still on therapy
89.	1997	Vin-Christian K	3	3		corticosteroids / vincristine / interferon-alpha / radiation therapy	NA
90.	1997	Sarkar M	21	21		corticosteroids / radiation therapy / embolization / cyclophosphamide (3) or vincristine (1) with interferon-alpha (sum 4), interferon-alpha (14)	5 patients died
91.	1997	Deb GJ	1	1		surgery / interferon-alpha	36 months
92.	1993	Zukerberg LR	8	4	4	surgery (2), steroids (1), chemotherapy / ligation / interferon-alpha (1), surgery / radiation (1), embolization / steroids (1), none (1), interferon-alpha (1)	Recent-8 years 2 patients died

TA = tufted angioma

NA = not applicable

Nineteen studies with in total 53 KHE patients without KMP were found. Of these 19 studies published before the occurrence of the guideline in 2013, only a minority of patients was treated with prednisolone monotherapy. There could no reports be identified in which patients without KMP were treated with oral prednisolone monotherapy since the reported standard of practice. From the 10 patients without KMP in studies published after 2012 three had a surgical intervention only and one received no therapy (Table 1).

In total 79 studies patients with KHE and KMP were described. Combination therapy with corticosteroids and vincristine was found in 38 studies with 111 KHE patients with KMP. After the publication of the guideline, 69 patients in 14 studies were found for whom the proposed combination therapy with corticosteroids and vincristine was at least used.

Case series in the Netherlands

Demographics

Thirty-nine patients were identified in the initial search. Of these, two patients were excluded because of insufficient clinical information. Furthermore three patients were excluded who had a diagnosis of angiosarcoma, tufted angioma and infantile multifocal hemangioma of the liver, respectively. In total, medical records from 34 patients were analysed in detail (Table 2). KHE was found ≤ 1 month of age in 15 cases (44%). The median age of initial presentation was two months (range, birth to 32 months). There was a male predominance in our cohort (25 male versus 9 female patients). One patient was lost to follow up.

Table 2. Patient characteristics and clinical outcome

	Age at diagnosis	Year of therapy	M/F	Presenting symptom	Lesion location	KMP	Center	Treatment	Alive
1.	4 months	1993	M	Enlarging mass	Upper extremity R	Yes	A	P	Yes
2.	1 month	1997	F	Feeding problems (abdominal distension)	Torso (PA)	?	B	Su	Yes
3.	***birth***	***1997***	***F***	***Enlarging mass in utero***	***Liver (PA)***	***Yes***	***B***	-	***No***
4.	3,5 months	1998	M	Enlarging mass	Facial R (PA)	Yes	D	P, IA, Em, V	Yes
5.	birth	1999	M	Enlarging mass	Lower extremity L	Yes	D	P, V, Em	No
6.	28 months	2000	M	Petechiae and bruising and enlarging mass	Cervical R (PA)	Yes	C	MP, V, IA	Yes
7.	1,5 months	2000	M	Enlarging mass	Lower extremity L (PA)	Yes	D	P, V	Yes
8.	2 months	2001	F	Enlarging mass and respiratory distress	Cervical L	Yes	D	P, V	Yes
9.	2 months	2001	M	Enlarging mass	Torso buttock L (PA)	Yes	E	MP, P, IA	Yes
10.	birth	2001	M	Enlarging mass	Torso	Yes	D	P, V	?
11.	***32 months***	***2002***	***M***	***Hepatospleomegaly***	***Liver and spleen (PA)***	***No***	***E***	***Su***	***Yes***
12.	***10 days***	***2002***	***F***	***Enlarging mass***	***Liver (PA)***	***No***	***E***	***Su***	***Yes***
13.	2 months	2003	M	Enlarging mass	Lower extremity R (PA)	Yes	A	P, V	Yes
14.	***birth***	***2004***	***M***	***Abdominal distension***	***Liver***	***Yes***	***D***	***P***	***Yes***
15.	2 months	2004	M	Enlarging mass	Lower extremity R (PA)	Yes	A	V, P, Su	Yes
16.	3 months	2005	M	Enlarging mass	Facial L (PA)	Yes	A	P	Yes
17.	***3 weeks***	***2006***	***M***	***Abdominal distension***	***Liver***	***Yes***	***E***	***P, V, Em, RT***	***No***
18.	***2 months***	***2007***	***M***	***Bleeding***	***Liver (PA)***	***Yes***	***D***	***P, V***	***Yes***

Table 2. Patient characteristics and clinical outcome (continued)

	Age at diagnosis	Year of therapy	M/F	Presenting symptom	Lesion location	KMP	Center	Treatment	Alive
19.	***1 month***	***2007***	***M***	***Abdominal distension***	***Liver***	***Yes***	***B***	***V, P***	***No***
20.	***5 months***	***2008***	***F***	***Coincidental finding***	***Liver (PA)***	***No***	***E***	-	***Yes***
21.	birth	2009	M	Enlarging mass	Facial L (PA)	Yes	E	P, V	Yes
22.	1,5 months	2009	M	Enlarging mass	Torso (PA)	Yes	A	Pro, V	Yes
23.	***2 months***	***2009***	***M***	***Anemia and abdominal distension***	***Liver (PA)***	***No***	***E***	***Su***	***Yes***
24.	***6,5 months***	***2010***	***M***	***Hepatomegaly***	***Liver***	***No***	***E***	-	***Yes***
25.	3 months	2010	F	Enlarging mass	Torso L (PA)	Yes	B	V, P	Yes
26.	4 months	2011	F	Enlarging mass	Lower extremity L (PA)	Yes	D	P, V, Pro, S	Yes
27.	4 months	2011	M	Enlarging mass	Upper extremity L (PA)	No	D	P, V	Yes
28.	1 month	2011	M	Enlarging mass	Upper extremity L (PA)	Yes	B	Pro, V, P, IA, Em,S	Yes
29.	birth	2011	M	Enlarging mass	Upper extremity L	Yes	F	At, P, V, S	Yes
30.	***birth***	***2011***	***M***	***Hepatomegaly***	***Liver (PA)***	***No***	***E***	***Su***	***Yes***
31.	2 months	2012	M	Enlarging mass	Cervical L	Yes	D	P, V, S	No
32.	Birth	2013	F	Enlarging mass in utero	Lower extremity R	Yes	D	Pro, V, Em, P	Yes
33.	***birth***	***2014***	***M***	***Enlarging mass in utero***	***Liver***	***Yes***	***D***	***P, V***	***Yes***
34.	***birth***	***2015***	***F***	***Enlarging mass in utero***	***Liver***	***Yes***	***F***	***P, V, S***	***Yes***

Abbreviations
MP = methylprednisolone, P = prednisolone, IA = interpheron alpha, V = vincristine, Pro = propanolol,S = sirolimus, At = atenolol, Su = Surgery, Em = embolization, RT = radiotherapy.
Italic bold *hepatic KHE patients*

Prenatal and late diagnoses

Four patients had lesions on prenatal ultrasonography that were diagnosed after birth as KHE. Patient 3 was diagnosed with a large tumor in the upper abdomen prenatally. After birth this patient had lung hypoplasia and high output cardiac failure due to arteriovenous shunting in the liver. Perinatal asphyxia occurred and the child died due to respiratory failure four hours after birth. Autopsy revealed a large KHE in the liver. Patient 32 was diagnosed antenatal with a tumor of the right lower extremity. Directly after birth a dilated left ventricle with mitral and tricuspid valve insufficiency was seen and KMP was diagnosed. Tumor biopsy at day one revealed KHE. Patient 33 showed a mass in the upper abdomen on prenatal ultrasonography. After birth KMP was diagnosed, KHE was suspected and the patient was treated with prednisolone and vincristine with good response. Patient 34 was also diagnosed with an intra-abdominal mass during prenatal ultrasonography screening. Lung hypoplasia and KMP were seen after birth. MRI revealed a large mass in the liver, which was suspected for KHE.
The latest referral of a patient diagnosed with KHE was at 32 months (patient 11). Symptoms of hepatosplenomegaly revealed two solitary liver and spleen KHE lesions.

Presenting signs and symptoms

Twenty-four patients had progressive enlargement of the tumor as a presenting symptom (71%). Other features were abdominal distension (n=5), hepatomegaly (n=3), anemia (n=1), bleeding (n=2), respiratory distress (n=1) and in one patient the KHE was a coincidental finding at ultrasonography.

Anatomic distribution

Nineteen patients had a cutaneous vascular lesion (56%); one patient had multifocal lesions, with one KHE lesion in the liver and one in the spleen. Five anatomic regions were defined to categorize KHE location: cervicofacial, upper extremity, lower extremity, liver (and spleen) and torso (including intrathoracic cavity and retroperitoneum, but exclusion of liver and spleen). KHE most frequently involved the liver (n=13; 38%), followed by the extremities (n=10; 29%), cervicofacial (n=6; 18%) and the torso (n=5; 15%).

KMP

Twenty-six patients (76%) showed symptoms of coagulopathy (bruising, petechiae, bleeding). Of those 26 patients with KMP, 22 patients (85%) showed a thrombocytopenia at presentation (platelets count <150x10E9/L, range <10 – 112x10E9/L). Four other patients revealed clotting disorders without thrombocytopenia. Of one patient the KMP status was unknown (patient 2). This child suffered from an upper abdominal mass, which was surgically removed at the age of one month.

Therapy

Several treatment options were used in our patient population over the years. Throughout the two decades prednisolone was most often used if systemic treatment was given (n=25 patients; 96%). In 21 cases (81%), at least a combination of prednisone and vincristine was given and in 20 of these patients, KHE was accompanied by KMP. Interferon alpha was used as a therapy merely during the late nineties (n=4; 15%) and no adverse events were reported, especially no spastic diplegia. Nowadays sirolimus and beta-blocker therapy are more often given (sirolimus in n=5 patients and propranolol / atenolol in n=5 cases). A surgical intervention was performed in six cases and five patients underwent embolization.

Three patients (patient 32, 33 and 34) were treated after the guideline was published. These patients suffered from KHE with KMP and were treated according to the guideline with the combination regimen of corticosteroids and vincristine (Table 2).

Mortality

Mortality rate in this cohort was 15% (five patients died): Patient 3 died of high output cardiac failure, respiratory insufficiency and perinatal asphyxia due to the KHE. Patient 5 died of an E. Coli sepsis and KHE with ongoing KMP (persistent thrombocytopenia), which led to an intracerebral haemorrhage. Patient 17 suffered from severe liver function failure, hepatic encephalopathy, myocardial hypertrophy, ongoing KMP, functional respiratory insufficiency because of the large abdominal mass, renal insufficiency due to cardiac forward failure, uncontrollable hypertension and a pseudomonas central venous catheter infection, to which he succumbed. Patient 19 died of multi organ failure and sepsis caused by the massive KHE and ongoing KMP despite treatment. Patient 31 died of sepsis and respiratory insufficiency most probable caused by pneumonitis during and probably as a complication of sirolimus maintenance therapy following successful prednisolone and vincristine induction therapy.

Discussion

KHE is a locally aggressive tumor that often is associated with KMP, a life threatening coagulopathy. Literature reveals many case reports with various treatment options. A consensus derived practice standards plan was published in 2013 (5). Our literature search revealed no case reports for patients with KHE without KMP on prednisolone monotherapy since 2013. Combination therapy with corticosteroids and vincristine for 69 patients with KHE and KMP was found in 14 studies since the publication of the guideline. In this study we present an overview of 34 Dutch KHE cases over the last two decades.

Most patients were diagnosed during infancy, sometimes even prenatally, with commonly an enlarging mass as first symptom. In a majority of patients KMP was found, with thrombocytopenia as the most important finding. Overall, treatment of choice was prednisolone, merely combined with vincristine. In the Netherlands three patients with KHE and KMP could be identified since 2013 and those patients were treated with the proposed combination therapy according to the guideline (5). Also before publication of the guideline most KHE patients with KMP were treated with the suggested combination therapy of prednisolone and vincristine in the Netherlands.

Before the recommendations of the expert meeting were published there was no consensus on treatment or standard protocols (5). The outcome of an expert survey by Tlougan et al., was used as a starting point for the consensus meeting in which the diagnostic work-up and treatment of KHE were proposed. The survey demonstrated that an interdisciplinary approach for the management of tumors with KMP was most commonly seen. Trends in treatment regimens favored the combination therapy of steroids and vincristine (4). During the consensus meeting in October 2011 the initial therapy for KHE without KMP was defined as oral prednisolone 2 mg/kg/day (5). The first line therapy for patients with KHE and KMP proposed is a combination of systemic corticosteroids and vincristine (5). Prednisolone 2 mg/kg/day or intravenous methylprednisolone 1.6 mg/kg/day was recommended and considered to be equivalent. Vincristine 0.05 mg/kg once weekly was added in the treatment combination. Mono-therapy was not advocated (5). Surgical resection or embolization should be reserved for treatment failure or for those KHE patients who have a life-threatening tumor (e.g. KMP and/or high output heart failure) that cannot wait for first-line treatment to be effective (5). To our knowledge the consensus derived practice standards plan is not yet systematically evaluated in a large patient cohort. Based on literature one cannot conclude that the recommendations of the guideline are used in daily practice. And although several reports were published since the publication of the guideline in 2013, many of those did not report on the outcomes of the proposed treatment, because different therapies were used.

A change in treatment can be observed in the literature and in the studied patient cohort from the Netherlands. In the late nineties interferon alpha was used in the therapeutic regimen of KHE, whereas currently apart from corticosteroid and vincristine therapy, beta-blockers and sirolimus are added. Vincristine became part of standard care after the study of Haisley-Royster et al., in which 15 patients with a vascular tumor received treatment with vincristine for KMP (6). All patients showed an increase in platelet count and in 13 patients a significant decrease in the size of the vascular lesion was reported. Most reported yet transient side effects were loss of deep tendon reflexes of the lower extremities and

abdominal discomfort (6).

Recently a phase II trial was performed to determine the efficacy and safety of sirolimus in patients with complicated vascular anomalies (7). Sirolimus was administered orally on a schedule with a starting dose of 0.8 mg/m^2 twice daily, with one course equivalent to 28 days. Sirolimus plasma levels were measured and were maintained between 10 and 15 ng/ml (7). The ten patients with KHE with KMP in this report all showed partial response to sirolimus. Partial response was defined as >20% reduction in size of the target vascular lesion evident on radiologic imaging or improvement in a target organ dysfunction by at least one grade or improvement of self-report PedsQol. Of three KHE patients without KMP, one patient showed partial response, one demonstrated stable disease and one had progression after six courses of sirolimus. After 12 courses two patients had partial respons and one still had progressive disease (7). Toxicity data attributed to sirolimus revealed blood/bone marrow impairment in 27%, metabolic/laboratory changes were found in 3%, gastrointestinal symptoms in 3%, infection in 2%, lymphatic disturbances in 2% and pulmonary/upper respiratory symptoms in 2% of patients (7).

It is sometimes difficult to distinguish KHE from other hepatic vascular tumors, which is highlighted in 13 patients in the Dutch cohort diagnosed with KHE in the liver. Hepatic involvement of KHE is controversial. In 2007 Christison-Lagay et al., showed more insight in infantile hepatic hemangiomas (IHH) and proposed three subtypes (8). Focal liver lesions are considered to be the hepatic equivalent of cutaneous rapidly involuting congenital hemangioma (RICH) and concomitant thrombocytopenia can be found (1). These vascular tumors are often asymptomatic, are Glucose transporter (GLUT) 1 negative and spontaneously regress (8,9). Multifocal lesions of IHH are most probable also asymptomatic although some can be associated with flow voids indicating the presence of arteriovenous shunts which may cause high output cardiac failure. Multifocal vascular tumors appear within the first weeks of life and often come to attention because of the presence of multiple (usually five or more) cutaneous infantile hemangiomas. These hepatic lesions follow the typical course of involution of cutaneous infantile hemangiomas and do demonstrate Glut-1 immunoreactivity (8,9). The final subtype is that of the hepatic diffuse lesions, which results in massive hepatomegaly, possible compression of the inferior vena cava and thoracic cavity, which in turn may cause respiratory symptoms. This mass effect can cause an abdominal compartment syndrome and multi-organ system failure. This type is also associated with severe hypothyroidism (8,9). Christison-Lagay et al. proposed a registry for IHH and in a follow up study the authors revealed that analysis of the liver hemangioma registry confirmed the proposed biological differences between focal, multifocal or diffuse hepatic hemangiomas (9). In retrospect, the 13 patients with hepatic involvement in our Dutch KHE cohort who were diagnosed and treated as KHE may very likely have been focal

hepatic vascular tumors. In recent years radiologists became more specialized in analyzing various vascular lesions especially with imaging modalities as MRI. Pathologists still have a tendency to report 'infantile hemangioendothelioma' from biopsy, while sub-classification seems more feasible now with Glut-1 immunoreactivity (8,9). In our opinion there is an urgent need for more close collaboration with radiologists and pathologists in order to align diagnostic classification (preferably according to ISSVA (1)), especially in hepatic vascular lesions.

Above described difficulties demonstrate the need for multidisciplinary expert teams in vascular anomalies to be involved in the care for pediatric patients with KHE. Representatives of these teams should be engaged in (inter-)national consensus meetings on this topic. In addition, similar to IHH, formation of an international registry is needed to validate the current guidelines and initiate a standardized second line treatment protocol. In the new recommendation sirolimus as a maintenance therapy after induction with the aforementioned first line therapy may be added to reduce toxicity. Treatment after failure of first line therapy should be case based, considering the efficacy of sirolimus, cyclophosphamide and beta-blockers, including embolization and radiotherapy as adjuvant therapies. Furthermore we propose to integrate an international clinical protocol with standardized care for vascular hepatic lesions, as this is lacking in the consensus derived treatment plan. Proper diagnosis of a vascular hepatic lesion as proposed by Christison-Lagay et al., should be followed (8). Corticosteroid monotherapy appears a rational first-line treatment if any therapy is indicated for vascular hepatic lesions. A KHE registry should also study long-term clinical outcome, side effects and adverse events.

To achieve international collaboration in daily care, digital data sharing is needed. To overcome this an electronic personalized health record would ideally realize real life analysis of clinical research data, regardless the patients' treatment location. This already exists for the care of patients with IH in the Netherlands (www.huidhuis.nl) and will soon be available internationally. While standardized clinical guidelines can be used in expert teams, data from the registry can be used by research groups. This can help to endorse experienced vascular teams in diagnosing vascular anomalies, further unravel pathophysiology of vascular tumors and optimize patient care, treatment and outcome.

Our cohort study has some limitations. Literature review suffered from the low level of evidence of the included studies, small sample sizes and lack of available data of therapy regimens or follow-up. Furthermore, retrospective data analysis of patients from other institutions over the last two decades showed gaps in medical records and limited follow-up information.

In conclusion, to gain more insight in the diagnosis and treatment of KHE, we reviewed the literature for KHE cases and analyzed all KHE patients in the Netherlands over the last two decades. To evaluate the current consensus derived practice standards plan, a prospective data collection integrated in a personal health record, as part of an international registry should be formed. Such a registry is vital to validate current treatment strategies; defining second line therapies and acknowledge hepatic vascular lesions as separate disease entity.

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Chapter 10

General discussion and future directions

In this chapter new insights into care and treatment of IH in children resulting from this thesis are integrated with known literature. Furthermore future directions for additional studies are proposed.

Part I Medical interventions for IH

How to address current medical treatment in IH?

IH are, unlike most birthmarks, uniquely dynamic, demonstrating a wide spectrum of disease with the natural tendency for involution. Predicting which infants need treatment or are at high risk for complications is a major challenge in the care for infants with hemangiomas (1). Both size and location are important parameters but the greatest single predictor of prognosis is morphologic subtype (1). Segmental hemangiomas are more likely to develop complications than localized hemangiomas. Even when controlled for size, segmental hemangiomas have a much greater need for monitoring and treatment (1). A proper diagnosis of IH should be obtained before initiating any therapy. This is especially true for systemic treatment with potential side and adverse effects. Furthermore any first-line therapy for IH must have shown to be more effective and safer than the standard therapy, especially in young developing patients. Propranolol rapidly became first-line treatment for IH based on serendipity, clinical observation, efficacy and tolerability in short-term studies rather than based on large (multicenter) RCTs with adequate long-term follow up and safety data. While propranolol has long been known and used in cardiology, its use in infants with IH had never been properly studied and there was no pharmaceutical form approved for pediatric use.

To date only two prospective randomized controlled trials for propranolol are available, which show efficacy, tolerability and short-term safety in clinical observations (2,3). It is remarkable that the RCT by Leaute-Labreze describes substantial involvement of the sponsor (Pierre Fabre Laboratories = PFL) in the study (3). PFL subsequently obtained an exclusive marketing authorization from the Food and Drug Administration (FDA) for Hemangeol, a medicine that contains the active substance propranolol, as the first and only approved treatment for proliferating IH requiring systemic therapy. The RCT findings were also supported by the European Medicines Agency (EMA), which also approved Hemangeol to treat children with proliferating IH (4). The agency's Committee

for Medicinal Products for Human Use (CHMP) decided that Hemangiols' benefits are greater than its risks and recommended its approval for use in the European Union (4). The committee concluded that Hemangeol was an effective treatment for hemangioma, with an acceptable safety profile in which risks are identified as those already known for propranolol and which can be appropriately managed (4). But data on long-term outcome in pediatric patients treated with beta-blockers for IH and other indications than IH, for example patients with arrhythmic diseases, are lacking. While there are concerns in the literature about for example the unknown significance of central nervous system (CNS) effects resulting from propranolol use in IH patients during early developmental stages and/or for prolonged periods of therapy, this information was not used as part of the phase III category registration of Hemangeol (5). Monitoring the safety of medication used in children is of importance since, during the clinical development of medicines, only limited data on this aspect are generated through clinical trials (6). The pediatric population represents continuing physiological changes both in body proportions and composition, growth and development (6). These changes in physiology and, consequently, in pharmacology, influences the efficacy, toxicity and dosing regimens of medicines used in children (6). The qualification of propranolol as a safe treatment strategy for IH in pediatric patients should therefore be interpreted with caution. To be able to judge the safety of propranolol, further research during early stages of development and long-term follow-up studies in children, for at least the first years of life, are imperative.

Although desirable in medical science, it is not always feasible to achieve the highest level of evidence for all treatment strategies. For some medications only limited evidence is available and pros and cons will be debated in literature. Awaiting more evidence, there is a certain general agreement for using these medications meanwhile in the best interest of the patient. Subject in future research and forthcoming updates of therapeutic guidelines should be the indications for using propranolol. In general treatment is indicated if IH cause life-threatening risks, functional impairment, local complications, like ulceration or bleeding. While Bauland et al., found no correlation between the growth patterns of an IH and the risk for a residual lesion, the epidermal invasion of the hemangioma proved to be more of a predictive value for residual lesions (7). Based on these data it might be doubtful whether beta-blockers will influence the residual lesion since they influence IH growth. Furthermore impairment of quality of life may be an indication for treatment, but this should be weighed with caution. Chamlin et al., showed the first results of quality of life measurements in parents and caregivers of children with IH (8). The clinical characteristics of IH with negative impact on quality of life (QoL) scores are IH located on the face/scalp/neck, those in the proliferative stage and larger sized lesions on the facial area/head/scalp. Parents of younger infants and those with infants with hemangiomas in the proliferative

stage have worse scores in the parent emotional functioning subscale (8). While the paradigm of efficacy is shifting towards propranolol treatment for less severe cases of IH the absence of information about possible long-term side effects and adverse events should be acknowledged. This is especially true for cosmetic indications, also because it is still unknown if the long-term outcome after treatment in cosmetic indications is favorable when compared to the natural course. Moreover in absence of information regarding cardiovascular, gross motor and neurocognitive outcomes, withholding propranolol therapy for pure cosmetic disfigurement in healthy infants with IH is advisable.

As we encountered adverse effects in patients with IH treated with propranolol (**Chapter 2**), the use of atenolol became of interest at our institution (**Chapter 3**). Our non-inferiority comparison study showed that atenolol therapy, based on the working mechanism of this hydrophilic selective beta 1 receptor blocker, might reveal less adverse events with at least the same efficacy as propranolol (**Chapter 4**). Another reason to initiate atenolol treatment was the ease of use with a probable better compliance as a result. Dissimilar to propranolol, atenolol has a terminal half-life of 6-8 hours and therefore can be dosed once daily (9,10). This and other preliminary studies indicate that hydrophilic beta-blockers such as nadolol and atenolol seem to be at least as effective against IH as propranolol (11,12). They might in the end turn out to be an even better alternative and the FDA and EMA should acknowledge these observations in their recommendations. Subsequently this also might prevent the hinder in funding research exploring alternative beta-blocker treatment than with the approved propranolol, only. Treating patients with atenolol might be needed as an alternative for patients that are non-responders following propranolol therapy or when patients might benefit from other working mechanisms or side effects profiles. A disadvantage of such non-inferiority research is that patients are being treated with 'only' non-inferiority medication. While this non-inferiority therapy is generally not assumed to be a better treatment than the treatment of first choice, it might be of important clinical relevance. Non-inferiority research might be seen as unethical, though providing treatment based on marketing or experience only, rather than on thorough evidence or the availability of safety and efficacy data, should actually be topic for an open debate. Treatment provided should be based on a conservative approach by physicians weighing all the above information even in the light of the persistent request of parents for treatment or the easy access to propranolol brought forward by the pharmaceutical industry.

Besides the importance to gain knowledge on propranolol therapy for IH, we should also learn from the decision-making by serendipity that took part in the acceptance of propranolol as first-line treatment in IH. The Oxford Dictionary of English defines serendipity as "the occurrence and development of events by chance in a happy or beneficial

way" (13). It is understanding this chance as any event that takes place in the absence of any obvious project (randomly or accidentally), which is not relevant to any present need, or in which the cause is unknown. The serendipitous can play an important role in the search for truth, but is often ignored in the scientific literature because of traditional scientific behavior and thinking based on logic and predictability. While propranolol should have been part of search for the highest level of evidence it was not identified as a serendipitous event, which could have generated important research ideas or reason to further discuss this unexpected event. Instead, propranolol was immediately adapted as a problem-solving satisfactory solution and first-line treatment in daily practice with limited evidence available. The pharmaceutical industry and authorities embraced that opportunity leaving some clinical physicians in despair while others, as early adapters, confirmed the innovation on its relative advantage without thorough evaluation.

Part II The pediatric perspective on IH treatment guidelines

How to acknowledge side and adverse events in a therapeutic IH guideline?

A guideline is a document with recommendations to support the medical professional and patients in aiming to improve quality of care, based on evidence based medicine and additional expert opinions of professionals and patients (14). Developing a guideline occurs in three stages in which several process steps are enclosed: preparation, development and completion (14). The preparation phase consists of defining the goal and the target group of patients. A working group of all interested parties is composed and all conflicts of interest have to be limited. During the developmental phase, an analysis of bottlenecks is defined, as well as the questions to be answered regarding etiology, screening, prevention, diagnostics, therapy, prognosis and/or health care organization. Analyzing a thorough review of the literature is essential during this second phase and serves as a basis for the recommendations in the guideline and the level of evidence. Subsequently it highlights gaps that currently exist and which might be addressed in future studies. In the final stage experts and patients are being asked to review the guideline, after which it will be authorized, implemented and evaluated. Evaluation of the guideline in daily practice often reveals useful information for amendments. A continuous cycle of development, implementation, evaluation, modification and maintenance is obligatory, while quality of care is the main objective (14).

The report of a consensus conference 'Initiation and use of propranolol for IH', stated that though propranolol had rapidly been adopted, there is significant uncertainty and divergence of opinion regarding safety monitoring, dose escalation and its use in PHACE (Posterior fossa, Hemangioma, Arterial lesions, Cardiac abnormalities, Eye abnormalities) syndrome (15). A multidisciplinary team reviewed existing data on the pharmacological properties of

propranolol and all published reports pertaining the use of propranolol in pediatric patients. Working groups were assigned to propose protocols on specific topics. Consensus protocols were recorded during the meeting and refined after the meeting. Because of the absence of high-quality clinical research data, evidence based recommendations were not possible at that time (15). However the conference attendees agreed on a number of recommendations that arose from a review of existing evidence, including contraindications and pretreatment evaluation protocols, initiation of propranolol in infants, cardiovascular and ongoing monitoring, awareness for bronchospasm and prevention of hypoglycaemia. The report stated that as there was considerable controversy, the more conservative approach was selected and while the recommendations were conservative in nature, revision should be undertaken as more data became available (15).

In more detail the pretreatment evaluation and monitoring of propranolol therapy from the consensus guideline determined a pretreatment electrocardiogram (ECG) if the heart rate (HR) is below normal, if arrhythmia is detected on cardiac examination or if there is a family history of arrhythmias or maternal connective tissue disease (15). Repeated cardiovascular monitoring in patients without comorbidity and normal vital signs was not advocated unless the dose of propranolol was altered significantly or during the first hours after therapy initiation, in correspondence with the peak effect of oral propranolol on HR and blood pressure (BP) one to three hours after administration (15). Despite these recommendations, the value and necessity of pretreatment screening and monitoring remained unclear, which prompted us to acquire cardiovascular data from all our IH patients treated with beta-blockers. The aim was to provide evidence-based data for future treatment recommendations (**Chapter 5**). Our study of cardiovascular data obtained following a pretreatment and monitoring protocol in IH patients receiving beta-blocker therapy, supported the aforementioned guideline. We demonstrated that in healthy patients without a significant family history and a normal HR and BP at initiation of beta-blocker treatment, ECG is probably of no additional value as a pretreatment screening tool. Additionally data from our report illustrated, in contrast with statements in the guideline, that dose response effects of beta-blocker therapy on BP occurred not only during initiation but also during follow-up. While asymptomatic hypotension during follow-up was not a reason to adjust therapy in this cohort, we are uncertain what influence this adverse effect has on these children's cardiovascular, gross motor or neurocognitive systems in the long term. Furthermore we stated that it is imperative for caregivers and professionals to be trained in recognizing all possible side effects of beta-blocker treatment in IH patients and to act accordingly. We systematically studied side effects and adverse events and found that more than 80% of the children suffered from side effects and adverse events, the vast majority of them being transient and mild. Information from this study should be used for the modification of the guideline from the consensus conference.

Only eight years after the first report of Léauté-Labrèze et al., detailed assessment of cardiovascular, gross motor and neurocognitive development has not yet been published in IH patients treated with propranolol (16). Subsequently short- and long-term development outcome of treated infants is unknown. Only one very recent study by Moyakine et al. showed that in 103 patients with IH treated with propranolol no evidence of psychomotor developmental delay was found (17). The authors concluded that it remains possible that propranolol treatment causes subtle adverse effects, which cannot be traced with tools such as the used van Wiechen scheme. And as such they suggest the use of universal screening tools such as the Parents Evaluation of Developmental Status (PEDS), the Ages and Stages Questionnaire (ASQ) or more advanced neuropsychological tests in future prospective studies in order to support their findings (17). Kwon et al. reported on the analyses of infants treated with propranolol for various indications, including IH (18). They demonstrated that no serious adverse events resulted in hospitalization, which supported the perceived safety profile of propranolol. Results also implied that serious adverse events might be delayed and thus not detected during initiation of the drug treatment (18). It is unknown whether young infants with IH and a normotensive cardiovascular system have a different complication risk of propranolol therapy compared to those infants treated with propranolol for cardiac indications. Another concern is the observation by Gonski, who noted that four of 84 IH patients with oral propranolol for IH demonstrated a delay in unassisted walking (19). In support of this, Langley summarizes many associated CNS effects of propranolol (20). This includes a meta-analysis of Lonergan, which demonstrates that propranolol treatment negatively influences recall of emotional material in healthy adults (21). Langley also refers to other adult volunteer studies that provide some support of impairments on psychomotor function, sleep quality and mood with relatively low doses and durations of propranolol (20). We endorse the concern raised by Langley about the unknown significance of CNS effects resulting from propranolol use in IH patients during early developmental stages and/or for prolonged periods of therapy. To objectively judge beta-blocker therapy in its safety in the light of the previous mentioned publications the current therapeutic strategy needs to be updated with new clinical data reviewing side effects and adverse events in short and especially long-term studies in children.

There is a wide range of seemingly less effective alternative medical therapies for IH, although high-level of evidence about agent, optimal dosage, treatment modality, pretreatment and treatment strategies is also limited for these. These strategies also demonstrate numerous side effects and adverse events during therapy, which are rarely systematically reported and long-term outcomes or sequelae are merely unknown. The possibility to exchange the short and long-term sequelae of, for example corticosteroids, into “acceptable” short-term adverse effects of beta-blockers seems to be more preferred by

clinicians, than the unsolved ravels of still unknown long-term side effects of beta-blocker therapy. And although literature reveals propranolol's effectiveness in 98% of cases, there are IH cases showing treatment failure or late proliferation of IH even months after a first positive response to propranolol (22, 23, 24). In order to guide the clinician in finding the most efficacious and safest treatment and monitoring approach for an individual patient, the list of therapeutic options for IH in children from literature was reviewed in our study in **Chapter 6**. This overview shows that head to head comparison studies are needed for effectiveness but also to compare side effects and adverse events in short and long-term. In absence of evidence-based literature it is hard to judge which is the most efficacious and safest therapy from the reviewed options. As such, therapy should ideally being withheld or at least only being used in specific cases and under supervision of expert teams in vascular anomalies.

Part III Wide spectrum of pediatric vascular lesions

How to achieve best care for the wide spectrum of pediatric vascular lesions?

Although IH is the most common benign vascular tumor in infancy, it is important to be aware of its occurrence in syndromes and its differential diagnosis. At birth IH are either absent or a precursor lesion, but they proliferate in the first few weeks to months of life, followed by an involution phase over several months to years (25). In many cases the appearance, time of onset, growth pattern and consistency of IH make the diagnosis straightforward (26). However experience is important to contrast IH with other vascular anomalies and even rare malignancies, especially early in life.

Describing vascular anomalies according to the International Society for the Study of Vascular Anomalies (ISSVA) is essential in the diagnostic phase (27). Mulliken and Glowacki proposed a classification in which behavior and natural history of vascular lesions are considered (28). This classification makes a distinction between vascular tumors, like IH, and vascular malformations and makes it possible to accurately classify vascular anomalies in up to 96% of patients. In 1996 the classification was slightly modified to reflect the importance of other types of vascular tumors that exhibit different clinical and histological characteristics than the common IH (including kaposiform hemangioendotheliomas, tufted hemangiomas and others) (29,30). This ISSVA classification was again updated in 2015 and is widely used by clinicians to differentiate vascular birthmarks (27).

In order to distinguish among vascular anomalies, it is important to understand the current classification into vascular tumors and vascular malformations. Biologically, vascular tumors are caused by endothelial cell proliferation, whereas vascular malformations are structural anomalies, inborn errors of vascular morphogenesis, with a normal endothelial cell turnover rate (31). Benign vascular tumors include congenital

hemangiomas, IH, tufted angiomas, spindle cell hemangiomas, epithelioid hemangiomas and pyogenic granulomas (27). Furthermore the ISSVA classification reveals locally aggressive or borderline vascular tumors such as kaposiform hemangioendotheliomas, but also malignant vascular tumors such as angiosarcoma (27). Whereas IH have a predictable life cycle, other vascular tumors vary both in onset and growth pattern. Vascular malformations are divided by type of vessel and speed of blood flow through the vessel, and they include capillary, venous, lymphatic, arteriovenous, and mixed malformations containing two or more of the above-mentioned vessel types (27). Many vascular malformations are combined and may occasionally coexist with other vascular tumors. Unlike IH, vascular malformations are often fully present at birth and grow proportionally with the patient, as he or she gets older (32). Most vascular malformations do not fade but instead become more prominent and occasionally thicker over time. Some vascular malformations do not present until later in life (32).

Segmental infantile hemangioma (SIH) of the face or neck is the PHACES syndrome hallmark. The underlying developmental abnormality that results in SIH remains to be determined (33). At present, a single cell lineage corresponding to these empirically defined segments has not yet been defined. However, the strong association of S1 lesions (fronto-temporal, with involvement of the lateral frontal and anterior temporal scalp) and CNS anomalies (especially cerebrovascular) points to a close interaction between progenitor cells that follow a cutaneous segmental course and the cells that govern the process of vasculogenesis, potentially mediated through the neural crest (33). At present it is not certain whether SIH develop along an entirely different or similar pathogenic course as localized IH. Besides cerebrovascular defects, cardiac anomalies are the most common extracutaneous features of PHACES. By determining the prevalence of IH for the diagnosis of PHACES syndrome in pediatric cases primarily diagnosed with obstructive aortic arch pathology (OAAP) in **Chapter 7,** we aimed for additional new or more detailed information to current literature. Unfortunately our retrospective cohort was limited in size to provide final conclusions and to proof an association.

In **Chapter 8** we report a case with a prenatally diagnosed congenital hemangioma, which reached maturity in utero and was monitored antenatal by ultrasound (US). More often vascular lesions are clinical diagnoses and radiologic imaging might help to further delineate vascular tumors and malformations. Hemangiomas typically exhibit a homogeneous, hypo-echoic signal, intense diffuse vascularity, and high flow on US-Doppler, which is not typical for other vascular tumors (34). High flow is typical for IH but also for (combined) arterial malformations, which can be further differentiated by magnetic resonance imaging (MRI). MRI typically reveals size and extensiveness of a lesion and gives insight in which blood

vessels are involved. Classic features are often found differentiating from other diagnoses without need for biopsy. Cystic lesions are more suggestive of lymphatic malformations, whereas calcifications are suggestive of venous malformations (35). Both findings can also be seen in teratomas. For MRI though often anesthesia is needed in young children and a disadvantage for US is that the accuracy is operator dependable. Biopsy can further confirm diagnoses based on typical histopathological characteristics. There are distinguishing histochemical endothelial markers, such as GLUT-1, which is present in IH but not in other vascular tumors (36). GLUT-1 is a facilitative glucose transporter protein (isoform 1) that is an important sensor for hypoxia. IH are vascular tumors in which benign endothelial like cells that possess these markers proliferate, the same process as seen on placental blood vessels (36).

Chapter 9 focuses on the therapeutic guideline for KHE patients with and without KMP published in 2013. In this consensus derived practice standards plan KHE is treated with prednisolone monotherapy, while first line therapy for KHE patients with KMP is a combination of corticosteroids with vincristine. Several case reports were reported since the publication of the guideline, though many of those did not show outcomes according to the proposed treatment, because different therapies were used. The Dutch cohort was merely treated with the suggested combination therapy for KHE patients with KMP. We suggest that a prospective data collection as part of an international registry should be performed to validate current treatment strategies. Subsequently modification of current therapeutic guidelines should involve a standardized second line treatment approach and a recommendation for sirolimus, which might be used as a maintenance treatment after induction with the combination therapy for KHE cases with KMP.

Expert teams in vascular anomalies need to be involved in the care for pediatric patients with vascular lesions. The team should at least be consulted once during the diagnostic phase of a child with a vascular lesion. To allow culmination of experience the number of expert teams in a country should be limited. Such a team should at least consist of a dermatologist, (plastic) surgeon and pediatrician, but when additional expertise is needed in extraordinary cases, for example orthopedists, gynecologists, radiologists, oncologists or ear nose and throat specialists should be involved. An expert team attendees' attitude ideally is open minded, collaborative and critical with regard to diagnosis, treatment and follow-up. Patient care should be case based with targeted therapy, in which the developing child is put in the center. During follow-up a shared or transmural care model is conceivable though the expert team should be easy accessible at all time for the treatment physician in shared care. Treating children with vascular anomalies should ideally be per protocol. Protocols and checklists have been shown to reduce patient harm through improved standardization and

communication (37). Furthermore their use, clearly have been demonstrated to improve outcomes (37). Standardized clinical guidelines should be used in expert teams, research groups but also in shared care models and at a national or if possible international level. This can help to endorse experienced vascular teams in diagnosing vascular anomalies, to further unravel pathophysiology of vascular tumors and optimize patient care and treatment.

Future directions

The pediatric perspective on IH treatment should be more highlighted in future clinical studies, as the study population consists of the developing healthy infant with a normotensive cardiovascular system. Conflicts of interests and dependency of pharmaceutical industries should at all time be restricted. First effort should probably be head to head comparison studies with beta-blockers, necessary to confirm (long-term) clinical outcome but also evaluating and comparing side effects and adverse events in short and long-term. Concentration of care in expert teams is needed and these teams should be represented in (inter-)national consensus meetings. These meetings with all interested parties are necessary to review literature and to select which questions should be answered in future research protocols. Continuously, international collaboration in standardized treatment and research monitoring protocols will be essential to draw conclusions from large data sets over time. To achieve international collaboration in daily care digital data sharing is needed. To overcome this an electronic personalized health record would ideally realize real life analysis of clinical research data, regardless of the patients' treatment location. This already exists for the care of patients with IH in the Netherlands and will soon be available internationally (www.huidhuis.nl). As such concentration of care, coordinated by the expert teams, creates the possibility of shared or transmural care for patients (38). Furthermore, frequent interim analysis reports are imperative for a continuous cycle of modification of protocols and guidelines, optimizing quality of care in the treatment of IH.

In conclusion the care for pediatric patients with hemangiomas should be based on a proper diagnosis of IH and a justified indication for therapy. A multidisciplinary expert team is involved in this process and judges the most evidence based efficacious and safest treatment and monitoring plan for each individual patient. A standardized long-term follow-up program for these patients is the basis for more insight in the pathophysiology of IH and further development and modification of guidelines, especially with regard to side effects and adverse events. Sharing results with other vascular anomalies expert teams and open communication, not driven by anything else than the patient, should be the focus for future directions.

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Chapter 11

Summary

Infantile hemangiomas are the most common benign vascular tumors in infancy. Most often IH follow an uncomplicated course without the need for treatment. However a minority of patients experience complications that require a more active approach. A proper diagnosis made by an experienced vascular team of physicians is warranted to predict which infants need treatment. Nowadays beta-blockers are the first line treatment. The aim of this thesis was to further optimize care and treatment of IH in children.

Chapter 1 gives an overview of the treatment of IH in historical perspective. At first radiation therapy was used as an effective treatment but related complications as dystrophy, induction of cancer and growth retardation were recognized. Nowadays radiation therapy is only used with the lowest possible dose and after thoughtful consideration of other treatment options. Corticosteroids are only useful during the proliferative phase of IH with a fairly good response rate. Well-known short-term side effects of corticosteroids are considered to be reversible. Pulsed dye laser therapy in the treatment for IH is reserved for ulcerated IH and post-involution erythema and teleangiectasias. Immune modulators can be used in the treatment of IH, but some serious side effects and adverse events are reported and information from large cohorts is lacking. Vincristine, bleomycin and cyclophosphamide are cytotoxic agents used in the treatment for IH, but treatment protocols are not standardized. Surgical interventions are used for functional impairment during the growth phase or for residual tissue following regression of IH. The beta-blocker propranolol is an effective and tolerated treatment of hemangiomas of which the safety is still to be elucidated.

Chapter 2 in Part 1 describes the results of the medical interventions we used for IH in our hospital. We conducted a study in which 28 patients were treated with propranolol for complicated IH. All patients showed a good response, even in the non-proliferative growth phase of IH and after the first year of life. In 17 patients side effects of therapy were found of which some were potentially harmful. Two patients had to discontinue propranolol treatment because of adverse effects, which might have been caused by the liphopilic and nonselective character of propranolol. The hypothesis that the use of a hydrophilic beta-1 antagonist could avoid the adverse events observed during propranolol therapy was studied in **Chapter 3**. In the two aforementioned patients atenolol was started, which was well tolerated, without adverse events and the hemangiomas responded well.

Chapter 4 shows the results of a comparison between two groups of patients, one treated with atenolol versus the previously described cohort treated with propranolol. In the atenolol group 27 of 30 patients showed clinical involution compared to all patients in the historical propranolol group. Side effects were less severe and less common in the atenolol group. We carefully concluded that this study showed that atenolol is as effective in the treatment of IH as propranolol, but atenolol seemed to be less frequently associated with potentially (life-) threatening side effects.

In part II the pediatric perspective on IH treatment guidelines is elaborated. **Chapter 5** reveals cardiovascular study data of 109 patients following a pretreatment and monitoring protocol. We demonstrated that baseline ECGs are probably of no additional value in patients without a cardiac (family) history and a normal HR and BP at start of beta-blocker treatment. It is probably more important to obtain an accurate cardiovascular medical history and thorough physical examination at consultation to identify patients with a contraindication for beta-blocker therapy. Furthermore we found that asymptomatic hypotension and significant decrease of BP can be missed following the recommendations of the consensus protocol. This is especially of importance while these observations are seen in furthermore healthy children with a normotensive cardiovascular system and while in literature concerns about the unknown significance of CNS effects from propranolol use in IH patients can be found. Our standardized questionnaires revealed over 80% reported side effects and this finding should be used as educational information for professionals and caregivers. **Chapter 6** is a review of the literature in which side effects and adverse events of treatment regimens for IH patients are evaluated. In total 254 studies were included with more than 10.000 patients treated with mainly five different therapy regimens. Therapies utilized demonstrate numerous side effects and adverse events known for their effect during therapy. High level of evidence is lacking and long-term outcome of these medications is unknown in IH patients. Furthermore we found that pharmacotherapeutic databases are incomplete in information regarding the treatment options in children with IH.

Part III shows that vascular lesions have an extensive differential diagnosis and can be associated with syndromes. PHACES is an acronym which refers to the medical findings of posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye anomalies, supraumbilical raphe and/or sternal pit, in which segmental hemangioma of the face or neck is a syndromal hallmark. Cardiac involvement is seen as aortic arch anomalies, in particular coarctation of the aorta. In **Chapter 7** we sought for PHACES in 286 children diagnosed with obstructive aortic arch pathology (OAAP) in our institution. In nine of 164 OAAP patients we found a hemangioma, of which one patient was already diagnosed with PHACES but no other patient

fulfilled the diagnostic criteria for definite PHACES. Unfortunately we were not able to recognize a significant association between the cardiovascular defects and PHACES. **Chapter 8** reveals a case report about another type of vascular tumor, a congenital hemangioma, which reaches maturity in utero. In this patient close antenatal evaluation by ultrasound and involvement of a multidisciplinary team warranted a proper diagnosis and treatment plan. **Chapter 9** shows that adherence to the current therapeutic guideline for KHE with or without KMP has not been studied so far. While most Dutch KHE patients are treated according to the therapeutic guideline, many cases from literature did not reveal outcomes according to the proposed treatment, because different therapies were used. This rare disease with high morbidity and mortality rate is in need for a prospective data collection as part of an international registry evaluating and modifying the current therapeutic guideline.

In conclusion results of the studies described in this thesis showed that propranolol is an effective treatment in patients with IH but that many patients encounter side effects of this therapy. Atenolol became of interest at our institution based on its alternative working mechanism. It subsequently showed similar efficacy and probably less (severe) side effects in comparison to propranolol. Furthermore we confirmed that an ECG is probably of no additional value as baseline assessment in otherwise healthy patients without a cardiac (family) history and a normal HR and BP at the start of beta-blocker treatment. We suggest that dose response effects of beta-blocker therapy on BP were seen during start *and* follow up. Furthermore we found that side effects and adverse events during propranolol treatment are commonly seen. Evaluation of this pediatric perspective serves as important information for modification of the current clinical guideline for propranolol therapy. Knowledge about propranolol used for cardiac indications or based on adult patients does not apply for the very young healthy pediatric patients with IH. And as such the safety profile of propranolol is discussed based on the concerns in the literature regarding CNS effects and the lack of long-term information on clinical outcome. Unfortunately serendipity in the discovery of propranolol was not recognized, while it was otherwise probably used for further research before it was regarded first line treatment.

An overview of therapeutic options for IH in children was presented to guide physicians in finding the most effective and safe treatment and how to monitor each individual patient with IH. Other medications used in the treatment of IH are probably less effective, information about side effects and long-term outcome is also lacking and precise information from adult pharmaceutical databases is incomplete.

Because of the wide spectrum of vascular lesions it is of great importance to concentrate clinical care for patients with for example PHACES, congenital hemangioma and KHE,

in a limited number of centres. The participants of expert teams serve at least as a reference regarding diagnosis, they should indicate further investigations and take a lead in harmonization and evaluation of therapy. Furthermore they should be collaborators to standardize clinical care and research internationally.

Samenvatting

Infantiele hemangiomen (IH) zijn de meest voorkomende goedaardige vasculaire tumoren op de kinderleeftijd. De meeste IH kennen een ongecompliceerd beloop en het beleid is dan ook in het algemeen afwachtend. Een klein deel van de kinderen met IH ontwikkelt complicaties en dit vraagt om een actieve benadering. Een multidisciplinair team met ervaring in vasculaire tumoren stelt de diagnose en beslist daarmee welke kinderen behandeling nodig hebben. Bij behandeling gaat de voorkeur uit naar het gebruik van beta-blokkers. Doel van het onderzoek dat in dit proefschrift wordt beschreven was om de zorg en behandeling voor kinderen met IH te optimaliseren.

In **Hoofdstuk I** wordt een historisch overzicht gegeven van de behandeling voor IH. Aanvankelijk werden hemangiomen effectief behandeld met bestraling totdat de bijwerkingen, zoals dystrofie, risico op kanker en groei vertraging, daarvan duidelijk werden. Bestraling wordt nu alleen nog gebruikt wanneer er geen andere behandelopties zijn en dan alleen met de laagst mogelijke bestralingsdosis. Hemangiomen in de proliferatie fase tonen een goede respons op de corticosteroïden, waarvan de kort termijn bijwerkingen over het algemeen reversibel zijn. Lasertherapie wordt voornamelijk gebruikt bij geulcereerde hemangiomen of als behandeling van restlesies van hemangiomen, zoals erytheem en teleangiëctasieën. Immuun-modulatie medicijnen zijn werkzaam tegen IH maar tonen soms ernstige bijwerkingen en er zijn weinig studies gedaan in grote groepen patiënten. Ook chemotherapie (vincristine, bleomycine en cyclofosfamide) wordt gegeven als IH behandeling, maar er zijn geen gestandaardiseerde protocollen. Chirurgische interventie kan soms nodig zijn in de vroege fase van behandeling, bijvoorbeeld als er functionele belemmeringen zijn in de groeifase van een hemangioom. In een later stadium wordt chirurgie soms aanbevolen als het gaat om het weghalen van restweefsel van het hemangioom wat in regressie is gegaan. De beta-blokker propranolol is een effectieve behandelmethode die goed verdragen wordt, maar waarvan de veiligheid voor de patiënt nog onopgehelderd is.

Hoofdstuk 2 in deel 1 beschrijft de resultaten van een klinische studie bij patiënten met IH. Een cohort van 28 kinderen met IH werd behandeld met propranolol. Alle patiënten toonden een goede respons op de behandeling, ook bij hemangiomen na de proliferatie fase of bij kinderen ouder dan 1 jaar. We lieten zien dat 17 patiënten neveneffecten ondervonden van de behandeling, die soms zelfs ernstig van aard waren. Twee patiënten moesten door deze bijwerkingen de propranolol behandeling staken. We veronderstelden dat de bijwerkingen te verklaren waren door de lipofiele en niet-selectieve kenmerken van propranolol. Met dat in gedachten genereerden we de hypothese dat atenolol, een hydrofiele beta-1-antagonist, wellicht deze bijwerkingen niet zou geven. **Hoofdstuk 3** beschrijft de

behandeling met atenolol van de twee eerder genoemde patiënten die door de bijwerkingen de propranolol niet verdroegen. Atenolol werd door deze twee patiënten goed verdragen, er werden geen bijwerkingen gezien en de hemangiomen reageerden goed op de therapie. Vervolgens vergeleken we in **Hoofdstuk 4** een cohort patiënten die behandeld werden met atenolol met het cohort kinderen uit hoofdstuk 2, dat propranolol kreeg. We konden laten zien dat van de 30 kinderen met IH die atenolol kregen er 27 klinische involutie hadden van het hemangioom in vergelijking met alle patiënten van de historische propranolol groep. In de atenolol groep waren de bijwerkingen minder ernstig en minder frequent voorkomend. De voorzichtige conclusie was dan ook dat deze studie aantoonde dat atenolol net zo effectief was als propranolol in de behandeling van IH, maar dat atenolol waarschijnlijk minder vaak potentieel schadelijke of levensbedreigende bijwerkingen gaf.

In deel II wordt een kindergeneeskundige kijk gegeven op de richtlijn ontwikkeld voor de behandeling van IH. **Hoofdstuk 5** presenteert de cardiovasculaire resultaten van 109 patiënten die volgens ons behandelprotocol onderworpen werden aan onderzoeken voorafgaande aan de behandeling met beta-blokkers en het onderzoek bij deze kinderen tijdens de behandeling. De resultaten toonden dat een ECG als uitgangswaarde voor behandeling meest waarschijnlijk niet van waarde is als patiënten geen afwijkende cardiale (familie) anamnese en een normale hartslag en bloeddruk voor start van de behandeling hebben. We suggereerden dat het belangrijker is om een accurate cardiovasculaire anamnese en een volledig lichamelijk onderzoek te verrichten als je patiënten met een potentiële contra-indicatie voor beta-blokkers wilt identificeren. Daarnaast toonden we dat asymptomatische lage bloeddruk en significant lage bloeddruk gemist kunnen worden tijdens de follow-up als de consensus richtlijn voor het gebruik van propranolol gevolgd wordt. Dit was een belangrijke bevinding aangezien het een bloeddruk daling betreft bij gezonde kinderen met een normotensief cardiovasculair systeem en in de wetenschap dat er in de literatuur zorgen worden geuit over de onbekende werking van propranolol op het centraal zenuwstelsel bij IH patiënten. Tenslotte lieten we zien dat wanneer je gestandaardiseerd naar bijwerkingen vraagt er in meer dan 80% van de kinderen bijwerkingen gemeld worden. Deze bevindingen moeten aanleiding zijn om kennis hierover te delen met professionals en verzorgers van de kinderen met IH.

Hoofdstuk 6 geeft een overzicht van de bijwerkingen van behandelingen voor IH uit de literatuur. In totaal identificeerden we 254 studies met meer dan 10.000 patiënten onder te verdelen in 5 verschillende behandelregimes. Veel van deze therapeutische opties tonen bekende bijwerkingen tijdens de behandeling. Echter evidence based onderzoek is schaars en de langetermijneffecten van deze medicatie werden veelal niet onderzocht in de IH patiënten populatie. Verder konden we vaststellen dat de farmacotherapeutische databases incompleet waren met betrekking tot informatie over de medicatie voor kinderen met IH.

Deel III van dit proefschrift beschrijft de uitgebreide differentiaal diagnose van vaatafwijkingen en hun voorkomen in bepaalde syndromen. PHACES, een acroniem voor afwijkingen in de achterste schedelgroeve, hemangioom, arteriële anomalieën, cardiale defecten, oog afwijkingen en supra-umbilicale raphe of sternumlesie, wordt gekenmerkt door een segmental hemangioom van het gelaat of hals. Cardiaal is er vaak een afwijking van de aorta boog, waarvan de coarctatie van de aorta het meest voorkomt. In **Hoofdstuk 7** bestudeerden we de gegevens van 286 kinderen gediagnosticeerd met een obstructie van de aorta boog om te zien of ze ook kenmerken van PHACES hadden. Negen kinderen in de groep van 164 patiënten hadden een hemangioom, van wie een patiënt de diagnose PHACES al had. In dit cohort kon geen significante associatie tussen een obstructie van de aortaboog en PHACES worden vastgesteld. **Hoofdstuk 8** is een case report van een ander type vaattumor, een congenitaal hemangioom, dat prenataal reeds aanwezig is. De diagnose en het behandelplan volgden uit overleg in een multidisciplinair team en de patiënt werd met behulp van echografie tijdens de zwangerschap en daarna gevolgd.

In **Hoofdstuk 9** wordt beschreven dat het gebruik van de huidige behandelrichtlijn voor KHE met of zonder KMP nog niet terug te vinden is in de literatuur. Ondanks dat de Nederlandse KHE cases wel volgens de richtlijn werden behandeld, rapporteren de cases gevonden in de literatuur niet of nauwelijks uitkomst van de therapie volgens de richtlijn, omdat veelal hele andere therapieën werden gebruikt. Deze zeldzame aandoening kent een hoge morbiditeit en mortaliteit en om die reden is een prospectieve data verzameling als onderdeel van een internationale registratie van belang om de huidige behandelrichtlijn te kunnen evalueren en aanpassen.

Concluderend tonen de studies in dit proefschrift dat propranolol een effectieve behandeling is voor patiënten met IH, maar dat veel patiënten ten gevolge van die behandeling bijwerkingen ondervinden. Atenolol zou een alternatief kunnen zijn omdat het een ander werkingsmechanisme heeft en wij konden laten zien dat het net zo effectief was maar waarschijnlijk minder frequent (ernstige) bijwerkingen geeft in vergelijking met propranolol.

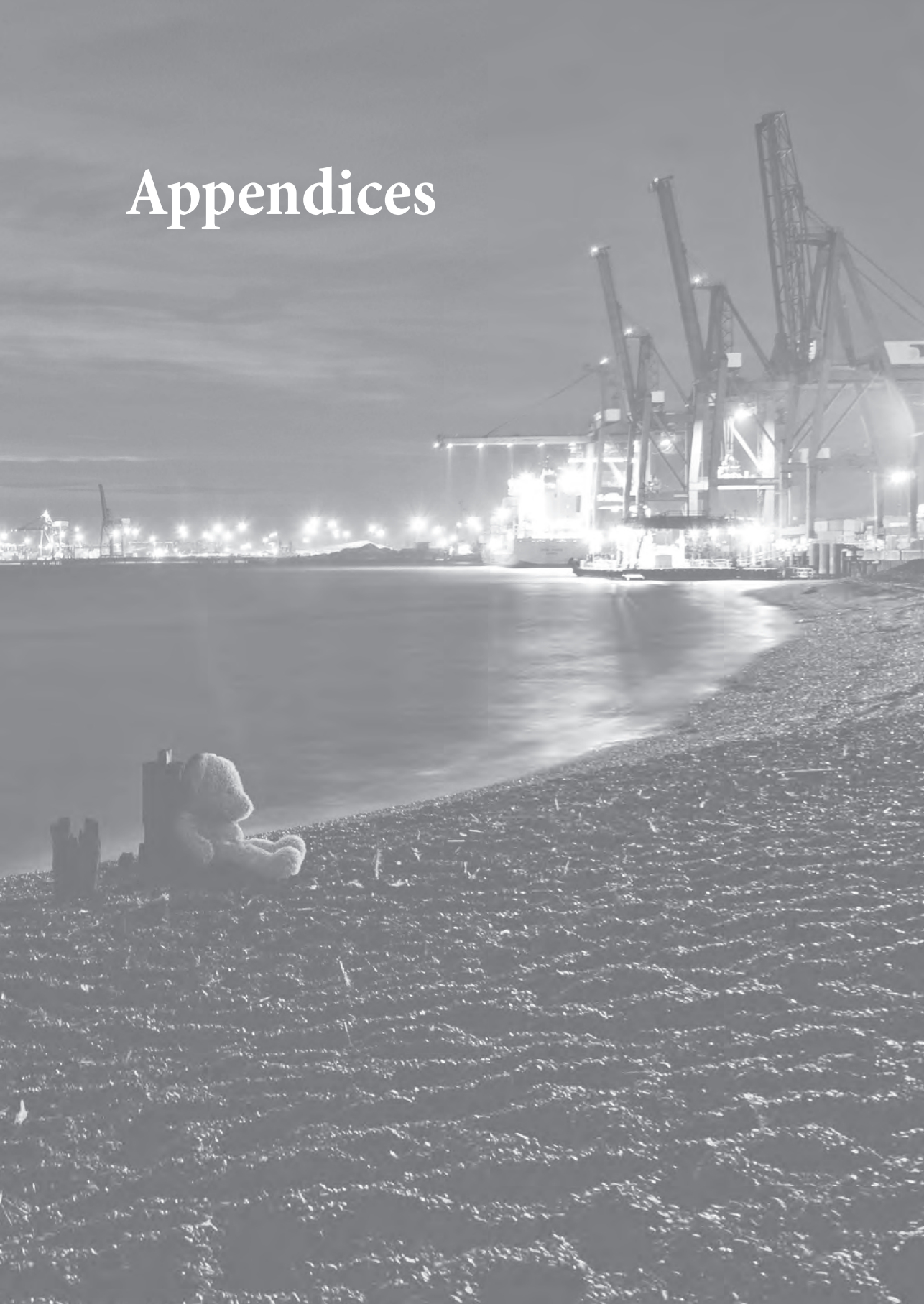
Verder toonden we dat een ECG niet additioneel is als uitgangswaarde bij gezonde kinderen met IH zonder een belaste cardiale (familie) anamnese en een normale hartfrequentie en bloeddruk voor start met een beta-blokker. We lieten zien dat de effecten van behandeling op de bloeddruk van een beta-blokker zowel tijdens start als gedurende de follow-up evident kunnen zijn. Tevens zagen wij dat meer dan 80% van de kinderen bijwerkingen ondervonden van de beta-blokker therapie. Deze kindergeneeskundige evaluatie van onderzoeken levert belangrijke informatie op waarmee de huidige richtlijn voor het gebruik van propranolol bij hemangiomen kan worden aangepast. Kennis over propranolol

uit de literatuur bij volwassen of bij kinderen met een cardiovasculair probleem zijn niet te vertalen naar de gezonde IH populatie. Het veiligheidsprofiel van propranolol staat dan ook nog ter discussie op basis van het gebrek aan informatie over langetermijneffecten en de aanwijzingen over CZS bijwerkingen van beta-blokkers in de literatuur. Helaas is het feit dat propranolol ontstaan is als serendipiteit niet erkend, want anders zou dit eerst tot verder onderzoek hebben geleid alvorens het medicament te laten promoveren tot eerste lijn therapie.

Als hulpmiddel voor de behandelaren werd een overzicht van therapeutische mogelijkheden voor IH in kinderen gegenereerd uit de literatuur. Focus hierbij was om de effectiviteit, veiligheid en het monitoren van IH patiënten tijdens behandeling te analyseren ten behoeve van het maken van keuzes voor de individuele patiënt. Andere medicijnen dan beta-blokkers zijn waarschijnlijk minder effectief en informatie over bijwerkingen en langetermijneffecten zijn ook hier niet beschikbaar, ook niet in farmacotherapeutische databases.

De prevalentie van PHACES syndroom bij kinderen met een afwijking van de aortaboog, een case report over een congenitaal hemangioom en het beschrijven van kaposiform hemangioendothelioom waren onderdelen van dit proefschrift om het belang aan te geven te streven naar multidisciplinaire behandelteams in een beperkt aantal centra. Samenwerking op (inter-)nationaal nivo bij deze zeldzame en diverse groep van aandoeningen is belangrijk om alle facetten van zorg (diagnose, onderzoek en therapie) en research te standaardiseren, harmoniseren en evalueren.

Appendices



Abbreviations

Infantile hemangiomas (IH)
Vascular endothelial growth factor (VEGF)
Vascular endothelial growth factor receptor (VEGFR)
Vascular endothelial growth factor A (VEGF-A)
Pulsed dye laser (PDL)
Longer wavelength Pulsed dye laser (LPDL)
Beta-fibroblast growth factor (b-FGF)
Interleukin (IL)
Tumor necrosis factor alpha (TNFa)
Matrix metalloproteinase (MMP)
Mammalian target of rapamycin (mTOR)
Glucose transporter-1 (GLUT-1)
Deoxyribonucleic acid (DNA)
Randomized controlled trial (RCT)
Human brain microvascular endotherlial cells (HBMEC)
Renin-angiotensin-aldosterone system (RAAS)
Posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye anomalies, supraumbilical raphe and/or sternal pit (PHACES)
Obstructive aortic arch pathology (OAAP)
Kaposiform hemangioendothelioma (KHE)
Kasabach-Merritt phenomenon (KMP)
European Medicines Agency (EMA)
Committee for Medicinal Products for Human Use (CHMP)
Pierre Fabre Laboratories (PFL)
Food and drug adminstration (FDA)
Central nervous system (CNS)
Electrocardiogram (ECG)
Heart rate (HR)
Blood pressure (BP)
Quality of life (QoL)
Parents Evaluation of Developmental Status (PEDS)
Ages and stages questionnaire (ASQ)
International Society for the study of vascular anomalies (ISSVA)
Segmental infantile hemangioma (SIH)
Ultrasound (US)
Magnetic resonance imaging (MRI)
Infantile hepatic hemangioma (IHH)
Rapidly involuting congenital hemangioma (RICH)
Non-involuting congenital hemangioma (NICH)

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Curriculum Vitae

Martine Fabienne Raphael werd op 9 januari 1974 geboren in Rotterdam. Ze groeide op in Zwijndrecht en ging aldaar naar de basis- en middelbare school. In 1992 behaalde zij haar VWO diploma aan de Openbare Scholengemeenschap Walburg. In datzelfde jaar startte zij met haar studie geneeskunde aan de Universiteit van Amsterdam.

Na haar opleiding tot basisarts begon zij in 2000 als assistent geneeskunde niet in opleiding (AGNIO) op de afdeling kinderoncologie F8Noord van het Academisch Medisch Centrum (AMC) onder de bezielende supervisie van dr. Marianne van de Wetering. In 2001 werd ze assistent kindergeneeskunde in opleiding (AGIO) in het Juliana Kinderziekenhuis (opleider dr. Arda Derksen-Lubsen) en volgde ze het academisch deel van deze opleiding in het Leids Universitair Medisch Centrum (opleider prof. dr. Jan-Maarten Wit). De opleiding werd in 2006 succesvol afgerond. In de laatste fase van de opleiding tot kinderarts kon zij al starten met haar fellowship kinder-oncologie/-hematologie (opleider dr. Marc Bierings) in het Wilhelmina Kinderziekenhuis (WKZ). De stage solide oncologie werd in 2007 volbracht op de afdelingen kinderoncologie van het VU Medisch Centrum (VUmc) en AMC. In 2008 volgde haar registratie tot kinderarts-oncoloog/-hematoloog en werd zij opgenomen in de staf van de afdeling kinderoncologie van het WKZ.

In 2010 werd ze als kinderarts toegevoegd aan het Centrum voor Aangeboren Vaatafwijkingen Utrecht (CAVU)–team in het WKZ (oprichters prof. dr. Suzanne Pasmans en dr. Corstiaan Breugem). De klinische werkzaamheden binnen het CAVU leidden tot het onderzoek hetgeen onderwerp werd van dit proefschrift. In 2012 werd ze hoofd van het Centraal Bureau Stichting KInderOncologie Nederland (SKION) LAngeTERmijneffecten na kinderkanker (LATER) in Den Haag. De werkzaamheden als coördinator van het onderzoek naar langetermijneffecten combineerde ze met een promotietraject onder leiding van prof. dr. Moshe Kon (Universitair Medisch Centrum Utrecht) en prof. dr. Suzanne Pasmans (thans Erasmus Medisch Centrum). In 2014 kreeg zij de mogelijkheid om terug te keren aan het bed van de kinderoncologische patiënt in het VUmc. Zij maakte daar ook deel uit van de opleidingscommissie kindergeneeskunde. Na de verdediging van dit proefschrift zal zij haar werkzaamheden als kinderarts in het Onze Lieve Vrouwe Gasthuis (OLVG) Oost te Amsterdam voortzetten.

Martine woont met haar partner en hun twee kinderen in Amsterdam.