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Rare and complicated forms of infantile hemangiomas: new therapeutic outlooks.

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1. INTRODUCTION

Infantile hemangiomas (IHs) are frequently encountered in paediatric population. In fact, they represent the most common infantile neoplasm.

IHs are benign vascular tumors which affect 10-12% of infants by the first year of life; they are more common in girls more than in boys (3:1), with an incidence of 1%-2,6% in newborn babies.

They are very frequent in premature infants with low weight at birth (23%); furthermore, their incidence is increased when a placental trauma or placental complications (placenta previa, chorionic villous sampling and amniocentesis) occur during gestation. (1)

Natural history of IHs is characterized by a predictable pattern of progression through three phases: IHs are not usually present at birth, but they appear during the first days or weeks of life, then they are characterized by a rapid proliferation until 10th-12th month of life followed by a spontaneous involution, of variable duration, that usually leads to the regression of IHs. Sometimes IHs are preceded by precursors yet present at birth. They are going to develop to IHs during the following weeks or months.

Involution is characterized by progressive softening of the tumor and fading of the bright red color with development of multiple white-grey areas on the surface of IHs.

Regression can be complete in some cases, but in other cases, residual sequelae may persist, such as fibro-fatty residual tissue, scarring, atrophic skin and telangiectasias. From a clinical point of view, they appear as red or purplish-blue masses ranging in size from a few millimeters to several centimeters. They may be single (80%) or multiple (20%), with a

tense or soft consistency, more or less floating compared to the underlying layers and, basically, not painful.

Moreover, if they affect only the skin, they may be superficial and bright red colored; they are dark bluish if they are subcutaneous and if they involve both the skin and the subcutaneous tissues they are mixed.

They occur more frequently in the head and neck region (60%), followed by the trunk (25%) and limbs (15%). Usually superficial IHs complete their growth during the first 5 months of life, while deep IHs tend to grow longer.

Histopathologically, IHs are masses of proliferating and plump endothelial cells with high mitotic activity and narrow vascular channels. The endothelial cells expresses the placental markers GLUT1, the glucose transporter protein 1, CD14, CD32 and merosin, which differentiate IHs from other vascular anomalies and from normal skin. (2)

They must be differentiated from congenital hemangiomas, which are vascular neoplasms fully developed and present at birth, without the tendency to further growth. Congenital hemangiomas are GLUT1 negative and they can be classified into two types: RICH (rapidly involuting congenital hemangiomas) and NICH (non-involuting congenital hemangiomas).

RICH are large tumours which often reach 5 cm in diameter, bright red or purplish colored, with a central depression lined by telangiectasias and a different color compared to the edges. They are usually located in the head and limbs.

NICH are most often flat, localized in the limbs or face and they show telangiectasias.

IHs must be differentiated also from vascular malformations, (such a port-wine stains, kaposiform hemangioendothelioma, tufted angioma) and pyogenic granuloma.

2. PATHOGENESIS

Different hypothesis exist on the origins of IHs, but none of these by self are able to explain the development of all the different clinical forms of IHs; the pathogenesis of IHs is complex, not completely elucidated and it probably arises from an integration of all these theories.

Two major hypothesis are competitive: the intrinsic hypothesis and the extrinsic hypothesis.

As a result of some studies, the first suggests that IHs derive from a somatic mutation in one or more genes involved in endothelial cell proliferation. IHs may be arise from an uncontrolled clonal expansion of endothelial cells in the skin.

Studies showed that all hemangioma-derived endothelial cells present the same X-inactivation pattern, moreover proliferating hemangiomas present somatic mutations of vascular endothelial growth factor (VEGF-R) receptors.

The second theory suggests that growth factors, tissue hypoxia and alterations in the microenvironment may stimulate the hemangiomagenesis.

Hypoxia is a powerful inducer of vasculogenesis as an up regulator of GLUT1; placental hypoxia seem to correlate with IHs.

In proliferating IHs some growth factors and their receptors such as VEGF-R2, angiopoietin receptors Tie-1 and Tie-2, angiopoietin-2, are over-expressed, leading to an increased angiogenesis.

Finally, there is the theory that IHs may arise from the clonal expansion of cells derived from placental endothelial cells. Invasive procedures, such as chorionic villous sampling, have been suggested to increase the occurrence of IHs, because they cause dislodgment of placental cells which enter the circulation and embolize the developing

fetus. (3) Supporting this theory, many of the molecular markers of IHs are also expressed by normal placental fetal microvessesl: laminin, merosin, Lewis Y antigen, Fc gamma receptor II, GLUT1. Another molecule expressed in hemangioma endothelial cells is the type-3 iodothyronine deiodinase normally expressed in the placenta: this enzyme inactivates thyroid hormones, so it can be responsible for children's hypothyroidism in case of large hemangiomas. (4)

In spite of these scientific evidences, it is not still possible to conclusively establish that IHs derives from placenta.

3. RARE AND COMPLICATED FORMS OF INFANTILE HEMANGIOMAS

Large (diameters larger than 5 cm) or segmental facial and lumbosacral IHs represent rare but potential life-threatening forms of IHs.

When a large or segmental IH involves the face, some clinical and instrumental evaluations are mandatory to exclude a PHACES syndrome (Posterior fossae malformations, Hemangiomas, Arterial anomalies, Cardiac anomalies, Eye anomalies and Sternal defects) and/or airways involvement if the IH is localized in the beard region. In the case of a facial hemangioma an increase rate of visits and a rapid treatment may be necessary to avoid severe complications, functional impairment or disfigurement (periorbital and perioral IHs, auricular and nasal localization). IHs involving the periorbital area may cause amblyopia and strabismus, those localized in the nose (Cyrano) and in the ears may cause permanent alteration of the cartilage structure, finally, those localized in the lips may ulcerate with feeding difficulties.

Cutaneous IHs localized in the mandibular region are frequently associated with airways involvement, so even in apparent absence of airways symptoms, an otolaryngology evaluation and eventually a laryngoscopy must be performed.

Lumbosacral or perineal IHs may be a sign of underlying structural anomalies, especially spinal dysraphism and lipomyelomeningocele.

Some acronyms highlight different structural anomalies associated with IHs: SACRAL syndrome (Spinal dysraphism, Anogenital, Cutaneous, Renal and Urological Anomalies with Lumbosacral hemangioma), PELVIS syndrome (Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesico-renal abnormalities, Imperforate anus and

Skin tags), LUMBAR syndrome (Lower body hemangioma and other cutaneous defect, Urogenital anomalies, Ulceration, Myelopathy, Bone deformities, Anorectal malformations, Arterial anomalies and Renal anomalies).

Magnetic resonance (MRI) is the best evaluation to detect spinal abnormalities which interest about 50% of children with lumbosacral large hemangioma. In these patients MRI is more sensitive than ultrasound, but in children younger than 3 months even MRI may not be enough sensitive and the study must be repeated at 6 months of age.

When a child is affected by 5 or more IHs, diffuse neonatal hemangiomatosis and/or internal organs involving must be investigated.

Hepatic ultrasound, thyroid function and heart evaluation must be performed to exclude the rare complications consisting in hepatic massive involvement, severe hypothyroidism and congestive heart failure.

Furthermore, neonatal diffuse hemangiomatosis must be excluded: it is a rare, potential life-threatening condition, characterized by multiple cutaneous (more than 5) and visceral hemangiomas involving at least 3 organs, onset in the neonatal period and in absence of the malignant transformation.

Segmental extremity hemangiomas, finally, show a higher risk of complications such as ulceration.

The commonest IHs complications are ulceration and subsequent pain, bleeding and infection, impairment of physiological functions and possible disfigurement.

Ulceration is the most common complication (15-25% of IHs), it is usually preceded by an early whitening of the IHs surface (child aged less than three months, to differentiate the signs of IHs involution), and it occurs more frequently in segmental, large size, mixed subtype IHs and in

those localized in the lip, neck, anogenital area, mucosae and intertriginous folds.

Large size or segmental IHs are potentially life-threatening for their mass effect: they may cause compression or obstruction of internal organs with impairment of their functions. Periorbital IHs can compromise the vision, perioral and lip IHs can interfere with feeding and bulky IHs of the head, neck and ears may lead to positional anomalies such as torticollis.

IHs with facial distribution or involving breasts and genitalia may cause permanent unaesthetic disfigurement and risk of scarring. (5)

4. TRADITIONAL THERAPIES

Although the majority of IHs do not require intervention because they spontaneously regress without any risk of later complications, about 10-20% of IHs need early treatment.

Indications for active therapies are:

1) Risk of ulceration
2) Prevent and avoid life-threatening complications
3) Prevent or treat functional impairment or pain
4) Prevent unaesthetic disfigurement

Even if a labeled protocol for treating IHs does not exist, corticosteroids have been considered until now the first choice therapy.

Systemic steroid therapy (prednisolone and prednisone) is usually administered at 2-3 mg/kg/die in a single daily dose: this treatment is very effective during the proliferative phase of IHs. The commonest side effects are gastrointestinal disturbances and irritability, weight gain, Cushing's disease, hypertension, adrenal suppression and immunosuppression.

During this treatment patients need periodic clinical evaluation and monitoring of blood pressure, glucose levels and weight.

Steroid therapy can be performed also by intralesional administration (triamcinolone 10 mg/ml), especially for bulky IHs localized in the lip, nose and sometimes for periorbital lesions. Possible side effects are bleeding, skin atrophy and infection; for periorbital IHs some cases of retinal artery damage and consequently blindness have been described.

The mechanism of steroid treatment is not clear, but they probably act directly on hemangioma endothelial cells; some studies demonstrated that prednisolone inhibits angiogenesis.

Other medical treatments are considered as a second or third choice in case of IHs that do not respond to corticosteroids.

Interferon α (recombinant INF 2α and 2β) has an antiangiogenetic activity and it can be used for treatment of difficult hemangioma; it is administered with daily subcutaneous injections at dose of 1-3 million U/mq; its main side effects are transient neutropenia and fever, but it may cause irreversible neurotoxicity so its use is very rare.

Vincristine is a vinca alkaloid chemotherapeutic agent frequently used for treat haematological and solid tumor malignancies. It can be used for treatment of life-threatening IHs when other therapies have failed and for Kasabach-Merritt syndrome. It is administered intravenously at 1-1,5 mg/mq weekly.

Vincristine has many side effects and its use needs oncologists and haematologists collaboration.

Bleomicin is an antineoplastic antibiotic used for the treatment of solid tumours of the head and neck, lymphomas and testicular carcinoma. Bleomicin is administered intralesionally for the treatment of IHs and its main side effects are ulceration and hyperpigmentation. Its efficacy has been reported in different studies and it seems to be due to the inhibition of neovascularization. (6-7) Some studies have reported the effectiveness of cyclophosphamide in the treatment of complicated, life-threatening hemangiomas, after failure of corticosteroid therapy. (8)

Cyclophosphamide is another chemiotherapeutic drug usually employed for treat malignancies such as lymphomas, leukemia and solid tumors and some autoimmune disorders.

Other treatments are lasers therapy and surgery. Pulsed-dye laser and Nd:YAG laser are used for superficial component of IHs and for ulcerated

IHs. Pulsed-dye laser is also used to treat residual telangiectasias in involuted IHs.

Surgery is sometimes necessary for chronic ulcerated IHs, bulky and peduncolated IHs, for those which do not respond to medical treatment and to reduce fibro-fatty residuum after the involutive phase.

Topical traditional therapies consist of application of potent topical steroids used for superficial IHs or imiquimod cream. (9-10-11-12-13). Possible side effects of potent steroids are skin atrophy, striae and risk of systemic absorption; common side effects of imiquimod cream are crusting, irritation and ulceration.

The topical treatment of ulcerated IHs consists in the application of emollients associated with non-adherent dressings such as hydrocolloid or petrolatum impregnated gauze. Other treatments include metronidazole gel or cream and topical platelet derived growth factor gel.

Furthermore, it is very important to prevent and treat pain by using lidocaine 2-5% ointment applied 3-4 times daily directly on the ulceration.

5. BETA BLOCKERS AND HEMANGIOMAS

Propranolol is a non-selective beta-blocker, so it equally binds β1 and β2 adrenoreceptors leading to a reduction of heart rate and cardiac output. At the beginning, this effect is hampered by a peripheral vasoconstriction. Moreover propranolol causes reduction in blood flow and pressure.

Propranolol was the first beta-blocker used for the treatment of angina pectoris; in the 1950s it was invented by Sir James Black who received the Nobel Prize in Medicine for this reason in 1988. (14-15)

At present its use in children is licensed for the treatment of hypertension, cardiovascular diseases and thyrotoxicosis; propranolol has a very good safe profile and in children it is used in doses as high as 7 mg/kg/die. It has potential and well known side effects: the most common are hypoglycemia, hypotension, bradycardia, exacerbations of asthma and mood disturbances. After more than 40 years of propranolol utilization in children, no case of death or life-threatening complications have been reported. (16)

From June 2008 propranolol became increasingly popular for the treatment of infantile hemangiomas: Léauté-Labrèze *et al*. reported in a letter to The New England Journal of Medicine the antiproliferative effect of propranolol on infantile hemangiomas. (17)

This serendipitous discovery was an incidental finding: they observed the regression of large and life-threatening IHs in 2 children treated with propranolol for concomitant cardiac diseases. Furthermore, the authors decided to treat another 11 patients affected by severe and disfiguring IHs with propranolol. In all patients they observed a rapid clinical regression of IHs, supported also by ultrasound examination data

which demonstrated reduction in thickness and increased in the resistive index of vascularization of IHs. Sans *et al*. reported a follow up study on 21 additional patients successfully treated with propranolol. (18)

From the original publication in 2008, several papers (more than 150) emphasized the effectiveness of propranolol on IHs. Other beta-blockers such as acebutol and nadolol have also been used for IHs, but the majority of reports regard the propranolol. Numerous case reports and some case series have been published supporting the efficacy and safety of propranolol for IHs.

Laforgia *et al*. and Manunza *et al*. reported the efficacy of propranolol for IHs in 23 and 30 patients respectively. (19-20)

Qin ZP. *et al*. successfully treated 58 children affected by severe IHs with propranolol: only 1,7% had poor response to the therapy. (21)

Leboulanger N. *et al*. reported a multicentric, retrospective study of 14 children affected by airways IHs treated with propranolol. All hemangiomas regressed with noticeable improvement of the airways stenosis; recurrences were noted in 4 patients after an early interruption of therapy. Two of these patients developed a resistance to beta-blockers, in fact the IHs do not respond to re-introduction of propranolol. One patient presented a severe episode of asthma, so propranolol was stopped and successfully substituted with acebutol. (22)

Hogeling M. *et al*. described a small randomized controlled trial of 19 patients treated with propranolol and 20 patients treated with placebo, reporting the efficacy and safety of propranolol therapy. (23)

Propranolol was administrated at a dosage of 1 mg/kg/die divided into 3 daily doses for the first week then increased to 2 mg/kg/die divided into 3 daily doses. This study reports the efficacy and safety of this therapy: only 2 patients do not respond completely to the treatment. No

hypotension, hypoglycemia or bradycardia were observed, but cold extremities, sleep disturbances and dental caries were reported.

Schiestl C. *et al*. reported a retrospective study on 25 patients treated with propranolol for problematic IHs. Dosage was 1mg/kg/die in 3 daily doses for the first day, then increased to 2 mg/kg/die from the second day. All the IHs responded to propranolol, only 2 patients presented mild regrowth and darkening of color after stopping the therapy. Reported side effects were sleep disturbances in 2 children and anxiety in 1 child: these were mild, self-limited and transient. (24)

Holmes *et al*. described a prospective study on 31 patients affected by proliferating hemangiomas treated with propranolol. They reported a regression rate of 87%, rebound rate of 24% after cessation of treatment and little and transient side effects. All patients with rebound were re-treated succesfully with propranolol. (25)

Buckmiller *et al*. described 32 patients affected by IHs treated with propranolol revealing good response in 50% of patients, partial response in 47% and no response only in 3%. (26)

Zaher *et al*. reported the efficacy and safety profile of oral propranolol at the dosage of 2 mg/kg/die, divided into 3 doses, in the treatment of 30 children with problematic IHs: 60% of patients showed an excellent response, 20% a good response (reduction of more than 50% in the size of IH), 16,6% a fair response (reduction of less than 50% in the size of IH), and no response in 3,3% (one patient); 17,24% of patients showed rebound of growth after cessation of therapy. No side effects were observed. (27)

A large retrospective study describes 71 patients (from four different hospitals in Argentina and Spain) treated with oral propranolol at a dosage

of 2 mg/kg/die divided into 2 daily doses. The result of this study is that propranolol is a rapid, effective and safe therapy for IHs. (28)

Bertrand J. *et al*. reported a retrospective study on 35 patients treated with propranolol for severe IHs. Rapid improvement was observed while no serious side effects were collected. (29)

Katona G. *et al*. described a retrospective study on 22 children affected by head and neck IHs and treated with propranolol. They concluded that propranolol is a highly effective therapy, with rapid reduction of IHs during the first week of treatment followed by a slower improvement. (30)

Shupp JC. *et al*. reported a study on 55 children treated with propranolol for IHs. Dosage was 2 mg/kg/day for a mean duration of treatment of 5,8 months. Mean age at the beginning of therapy was 6 months. Eight patients showed a complete regression, 46 partial regression and 1 had no response. Thirteen patients showed some side effects, but only 1 patient needed an early withdrawal of the therapy for aggravation of preexisting bronchial asthma. Six patients showed recurrences after termination of the first course of therapy, so a second propranolol treatment was necessary. No relapses were observed after the second cycle of therapy. (31)

Gan Li *et al*. reported one of the largest retrospective study involving 109 Chinese patients treated with propranolol 2 mg/kg/day for IHs. Regression was observed in 108 patients, of which 19 showed complete regression while 89 partial regression. Only 1 patient had no response. Twenty-three children had some adverse but mild side effects and only 4 children needed an early therapy withdrawal. Relapses occurred in 9 patients who needed a second course with propranolol which was successful for all. (32)

Hermans D.J.J. *et al*. reported one of the largest prospective study on 174 patients affected by IHs treated with propranolol in the Netherlands. A target dosage of 2-2,5 mg/kg/day was administered to the patients: they observed a good response in 173 patients; only 4 patients required a second course of propranolol for recurrences and this second treatment was successful in all patients. Possible side effects were noted in 108 patients, but only 15 patients required a dose reduction while in 1 patient, with extreme nocturnal restlessness, propranolol was switched to atenolol, obtaining a better sleep and a good regression of IH. Only 1 patient, who was extremely premature, required early discontinuation of the therapy due to a severe hypotension, drowsiness and cold-extremities. The main side effects collected in this study were hypotension, wheezing especially during upper respiratory tract infections and sleep disturbances. (33)

Jian D. *et al*. performed a study on 97 Chinese patients treated with propranolol at dosage of 2 mg/kg/die for IHs, in order to assess the safety of this therapy. All patients were examined at follow up for a period from 6 to 12 months. Some side effects were reported: bronchial hyperreactivity, cyanosis and cold extremities, agranulocytosis and low body temperature. Most of these side effects appeared in the first week of therapy, period that needs the most strictly surveillance. (34)

Zvulunov *et al*. reported 42 patients affected by IHs successfully treated with propranolol beyond the proliferative phase, to indicate that this therapy is effective also in the post-proliferative phase. In this retrospective study only patients aged more than 12 months and those with IHs without signs of growth were enrolled. Median age of the patients in treatment was 22 months. Mean duration of the therapy was 3,6 months. The therapy was discontinued when the lesion stopped to respond to the treatment. Mild side effects were reported in 4 children consisting in sleep disturbances and

transient dyspnea. None of patients showed complete involution, but aesthetic improvement was reported in the whole group. This report allows to treat with propranolol every child with late IH residual, before a surgery. It is unclear how propranolol acts in the post-proliferative phase. (35) (These data are summarized in table 1)

All reported case series demonstrate the high efficacy of propranolol in inducing regression in IHs, even in those non responsive to corticosteroids or other therapies. Furthermore, propranolol therapy did not frequently show severe side effects, on the contrary to systemic steroids, INFα, vincristine and bleomicine.

The most common reported side effects are hypotension, pulmonary symptoms, hypoglicemia, bradycardia, sleep disturbances, cold extremities, gastrointestinal problems. Two cases of hyperkaliemia were reported.

A case of tumor lysis syndrome and hyperkaliemia after propranolol therapy in ulcerate IH was described in a 33-days-old child: it can be considered a rare complication of ulcerated IHs treated with propranolol. In the case reported no treatment or early propranolol withdrawal was necessary because the electrolytic alterations were mild and self-limited. (36)

Another case of severe hyperkaliemia was reported in a 17-week-old preterm girl affected by a large and ulcerated IH during the first days of propranolol intake. In this case, the patient required a further treatment to normalize the serum potassium level but did not require early propranolol discontinuation; the hemangioma successfully responded to propranolol. (37)

Nowadays a well standardized protocol for IHs treatment is lacking, as well as for the use of propranolol. The first consensus conference about the use of propranolol for IHs was performed in Chicago on December 9,

2011; a multidisciplinary team discussed and agreed on a number of recommendations arising from a review of existing evidence. (38)

Recommendations for the initiation and use of propranolol for IHs: only patients affected by IHs with high risks for complications must be treated.

Dermatological visit and recruitment for therapy, cardiological assessment with electrocardiography (ECG), blood pressure measurement and pediatric evaluation for blood glucose level and routine screening should be performed. For patients affected by PHACE syndrome, echocardiography, magnetic resonance (MRI) or angiography of head and neck area are mandatory. Every patient must be individually evaluated for risks and benefits of propranolol therapy. The propranolol treatment must be managed in close consultation with cardiologists.

Propranolol should be administrated into 3 daily doses, at the initially dosage of 1 mg/kg/die and after a week increased to 2-3 mg/kg/die if it is well tolerated. At the end of the therapy, propranolol should be gradually tapered in 2-3 weeks. The treatment should be performed through the proliferative phase of IHs or until regression. If rebound occurs, propranolol should be re-introduced.

Patients aged less than 8 weeks of gestationally corrected age or with comorbidities should be hospitalized for the start of the therapy, while patients over 8 weeks of gestationally corrected age do not require any hospitalization. All patients should be monitored with heart rate and blood pressure during the first hours after initiation and after every dose increase. In order to reduce risk of hypoglicemia, which is age-related, patients should be fed frequently (at least every 4 hours for the infants aged less than 6 weeks) and propranolol should be discontinued in case of illness.

Particular attention must be taken for preterms and for patients who need concomitant medications.

The mechanism of action of propranolol in the treatment of IHs is not clearly understood. Beta-adrenoreceptors are part of a G-protein coupled receptor super family, expressed on endothelial cells, which activate adenylate cyclase. This cascade of signals leads to a nitric oxide synthesis in the endothelial cells: this results in vasodilatation. Beta-blockers act blocking this signaling. The rapid changes observed in IHs during the first 48 hours are due to vasoconstriction due to the decreased release of nitric oxide. The intermediate effects of propranolol are due to a reduced expression of angiogenetic factors, which play a role in the endothelial cells proliferation, to a down-regulation on the renin-angiotensin axis causing a reduction of angiogenesis. The long-term effects are due to an up-regulation on the caspase cascade leading to induction of apoptosis. (39-40)

Until now several cases of recurrences after propranolol therapy have been reported, although the rate and the possible causes have not been explained. Regrowth of IHs after corticosteroid treatment is well-known and frequently reported. Concerning propranolol treatment, IHs with deep component seem to be more susceptible to recur after propranolol cessation.

Bagazgoitia *et al*. reported 26 patients treated with propranolol with a recurrence rate of 19% (5 patients), observed 9 months after the end of the therapy. The span of time from withdrawal to recurrence ranges from 0 to 6 months, 4 patients presented partial recurrence while 1 patient complete recurrence. Possible causes of recurrences were explained by authors: early therapy withdrawal (before the end of the proliferative

phase), but also a long proliferative phase; VEGF-R involvement and an incomplete apoptosis in the endothelial cells. (41)

It is clear that propranolol have to be administered until the end of the proliferative phase that in the majority of severe IHs occurred at 10th-12th month of age. However it is difficult to predict which IH will have a late proliferative phase, so it is very complicated to define a fixed protocol of treatment: the duration of the therapy must be individualized. IHs are very heterogeneous and their clinical evolution is unpredictable. The time of relapses after propranolol withdrawal is heterogeneous, so the patients must be followed for at least 6 months.

Izadpanah *et al*. reported a systematic review of the literature from 1965 to 2012 and a meta-analysis to compare the use of propranolol versus corticosteroids in the treatment of IHs, suggesting that propranolol therapy could be superior to the steroid therapy. (42)

Their results showed that less than 90% of patients treated with steroids responded to the therapy versus 99% of patients treated with propranolol. The meta-analysis demonstrated a resolution rate of 97% compared to 71% for propranolol versus systemic corticosteroids. The complication rate in the cases treated with steroids is more than double if compared to propranolol therapy.

Peridis *et al*. performed another meta-analysis and demonstrated the superiority in the effectiveness of propranolol and the less side effects versus the traditional therapy used in the airways hemangiomas treatment such as corticosteroids, laser CO2 and vincristine. (43)

Nowadays topical propranolol treatment is anecdoctal, but some cases of superficial hemangiomas have been successfully treated. Topical beta blocker is available in form of timolol solution 0,25% or 0,5% eyedrops or timolol maleate gel-forming 0,5% or 0,1%; moreover, a

galenic formulation propranolol cream 1% can be made. It must be applied twice a day on the hemangioma for a variable period in relation to the individual response. After the first case-report published in 2010 by Guo *et al*., regarding the utility of topical beta blockers in IH, especially timolol maleate, several case reports and some studies were described. (44-45-46-47)

The results are encouraging, timolol maleate seems to induce regression in the superficial component of IHs and it could be a substitute when systemic propranolol is contraindicated. However, timolol maleate as well as systemic propranolol, may cause side effects due to its systemic absorption. Even if the timolol maleate percutaneous absorption and its bioavailability on intact skin are unknown, however physicians who prescribe this drug must be aware of the signs and symptoms of potential systemic absorption. More important systemic absorption occurs when timolol maleate is applied near or on mucosal surfaces, on ulcerated hemangiomas and on thinner skin sites.

Gel-forming solution seems to be less absorbed and safer than timolol maleate solution for the treatment of IHs. Caregivers should be instructed to use one or two drops per application to avoid beta blockers overdose. Local cutaneous side effects due to topical timolol application are alopecia, localized or generalized rash, psoriasiform dermatitis and angioedema. (48)

6. OUR EXPERIENCE

From 2008 to 2012 in our Paediatric Outpatient Service of Dermatology of the University of Bologna, a pilot, monocentric, open label, not randomized and not controlled clinical study was conducted by a medical team made up of Dermatologists, Pediatricians, Radiologists and Cardiologists. Local ethical approval was obtained before starting the study. The main objective of the study was to determine the efficacy and the tolerability of systemic propranolol in the treatment of infantile hemangiomas.

Materials and methods:

All patients were enrolled after a dermatological examination which also included an iconography at baseline, in order to evaluate the inclusion and exclusion criteria.

Inclusion criteria:

- large and/or segmental IHs
- IHs in critical sites (e.g. ears, eyelids, nose and lips)
- rapid growth
- ulceration
- possible impairment of physiological functions
- possible evolution toward disfiguring scars
- written informed consent

Exclusion criteria:

- cardiovascular diseases
- asthma
- hypersensivity to propranolol in first degree
- diabetes mellitus

Before starting the treatment, all patients underwent both a cardiac evaluation including elettrocardiography, blood pressure measurement and baseline heart rate and pediatric evaluation with blood tests to check liver and renal functions and glucose levels.

Ultrasound evaluation, especially with echo color doppler, was usually performed to assess the deep component, the volume and the real extension of the lesion.

Patients affected by large or segmental facial IHs required head and neck magnetic resonance imaging (MRI), otolaryngology evaluation, sometimes with laryngoscopy if the segmental IHs involved the beard region, ophthalmological evaluation, echocardiography and thyroid examination to exclude PHACE syndrome. MRI was sometimes necessary to differentiate some IHs from vascular anomalies, to detect an internal involvement and to evaluate the deep extension. Moreover, MRI was necessary when the IHs were localized in the lumbosacral area; lumbosacral MRI, in children under the age of 3 months, could not have a good sensitivity , so the examination had to be repeated over time.

In case of multiple IHs, cerebral and hepatic ultrasound examination were usually performed to exclude the presence of internal hemangiomas.

The follow-up (consisting of dermatological evaluations with iconography) was performed weekly during the first month of therapy and then, monthly, until the treatment was concluded. All IHs were evaluated for color, volume and consistency and, in order to assess their evolution, a photographic comparison was carried out.

Moreover, all patients were evaluated by Pediatricians for a general examination every week for the first month, then monthly.

Cardiologists conducted examinations every month and electrocardiographies were performed every 3 months until the end of the treatment.

Usually, ultrasound examinations of the lesion were performed weekly at the beginning of the treatment and then monthly.

Recommended regimen doses varied from 1 mg/kg/day to 3 mg/kg/day divided into 3 daily doses. In our protocol, we usually started and continued with 2 mg/kg/day for the entire duration of the treatment; only in case of absence of improvement after 4 weeks, the dose could be increased by 0,5 mg/kg/day weekly up to 3 mg/kg/day. At the end of the treatment, propranolol was gradually tapered to 1 mg/kg/day per week. In some patients, especially in very young children, we started with 1 mg/kg/day and we gradually increased to 2 mg/kg/day. The duration of the treatment could be variable, relating to the IH features and to the single responses to propranolol. It is generally recommended to continue the therapy until the proliferative phase is finished, about up to 12 months of life, to avoid the risk of regrowth, although some relapses could occur after this period.

Results:

Seventy-eight patients (57 females and 21 males; 2.7:1) were enrolled in the study. Now, in 58/78 patients (45 females and 13 males) the treatment has been stopped, while 19 patients (11 females and 8 males) have been undergoing the treatment. One girl, after the enrollment, was lost at follow up.

Forty-two of the 58 patients who had completed the treatment had good results, without any side effects and recurrences. Six children, showed recurrences when the therapy was concluded despite a good response after the first cycle of treatment. They were re-treated with propranolol, for at

least 3 cycles, but 4 of these 6 patients did never show the complete regression of their IHs. Furthermore, they had a tendency for recurrences after the conclusion of every therapeutic cycle.

In our patients, the rebound of growth occurred after an average of 3 months (range 0-9 months) after the stop of the propranolol therapy. The first cycle lasted about 10 months and at the end of it the patients were aged on average 15 months.

These are the features of our 6 cases of relapses which needed a further therapy:

- 1) Girl, born at term, with submandibular IH: she started the propranolol therapy at 5 months of age, initially at dosage of 1 mg/kg/die for the first week, then it increased to 2 mg/kg/die and it was performed for 9 months (until she was 14 months old), with good regression. Nine months after the discontinuation of the therapy, because of a relapse, she re-started propranolol at the same dosage for further 6 months. The IH regressed and the patient has been in follow up for 6 months.
- 2) Girl, born preterm, with IH localized on her left cheek: she was initially treated with systemic steroid (deflazacort 2-2,5 mg/kg/die) with partial regression. At 9 months of age, she was treated with propranolol for 10 months (age of conclusion of the therapy: 20 months). Soon after the conclusion of the therapy a relapse occurred; the patient was re-treated with propranolol for a further 3 months but no improvement occurred, so the baby underwent a surgical treatment.
- 3) Girl, born preterm, affected by beard hemangioma involving the airways: propranolol therapy was started at 2 months of age with a good response both of the cutaneous and the airways components. Therapy was stopped at the age of 16 months. The lesion relapsed after 3 months, so that another propranolol cycle was prescribed for 3 months.

Eight months after the conclusion of the last cycle, regrowth occurred. The patient was surgically treated.

- 4) Boy, born at term, affected by a lip ulcerated IH: at the age of 2 months, he started propranolol therapy performed for 8 months (it was stopped at age of 10 months) with excellent results. However, after 3 months, a regrowth was noted and the therapy was re-introduced for 9 months (age 22 months) with only a partial regression of the lesion. After 6 months of follow up and a consultation in the maxillo-facial surgery division, a third cycle of propranolol was made for 10 months with further improvements. The patient is currently on follow up.
- 5) Girl, born preterm, affected by a right palpebral IH. She was treated with deflazacort 3 mg/kg/die for the first 3 weeks of her life. Propranolol was started at 1 month of age and extended up to 14 months of age with satisfactory results. Three weeks after the conclusion of the therapy, the lesion showed a regrowth, so the therapy was re-introduced for 3 months. One month after the conclusion of that second cycle, the lesion still relapsed and the therapy was prescribed again for another 3 months. The patient is currently on follow up, a mild IH residuum is still present and it should be object of surgical evaluation for aesthetical improvement.
- 6) Girl, born at term, affected by a latero-cervical IH. Propranolol treatment was started at 10 months of life and conducted for 5 months then it was stopped because of the good results obtained. However, after only 1 month, the lesion tended to regrowth, so further propranolol therapy was administered until the age of 21 months. Good results were obtained, except for unaesthetic residual changes which could be surgically treated after a surgeon consultation.

6/58 patients did not respond to the beta blockers: 4 patients underwent surgery treatment, 1 patient was treated with systemic

corticosteroid with poor response and 1 patient was treated with topical propranolol.

Features of the 6 patients:

- 1) Girl, born preterm, affected by a voluminous and ulcerated IH localized in the left parietal region. She had been treated with propranolol since the age of 5 months until 11 months. The superficial component of the IH regressed, the deep component did not respond to the therapy and a surgical treatment was suggested.

- 2) Girl, born preterm, affected by an ulcerated IH sited on her right arm: propranolol had been administered since the age of 7 months until the age of 14 months, initially at the dosage of 2 mg/kg/die and gradually increased up to 5 mg/kg/die without any response. An early (when she was 15 months) surgical treatment was suggested.

- 3) Girl, born at term, affected by a fast growing, ulcerated lip IH: at the beginning she was treated with corticosteroid (deflazacort 3 mg/kg/die) when she was 3 months old with partial response. At the age of 21 months she started propranolol, continued for 7 months. The lesion improved but it did not totally regress, so she was surgically treated.

- 4) Boy, born at term, affected by a deep periorbital IH. We performed a late intervention: the patient was 4 years old when a propranolol therapy was attempted for 2 months without any response. Then, the patient had a surgical treatment.

- 5) Boy, born preterm, affected by a facial segmental right IH involving palpebral area: propranolol therapy was started at 4 months of age at the dosage of 2 mg/kg/die for 1 month, then it was increased up to 3 mg/kg/die because of the absence of response. This dosage was extended until the first year of life without regression. The patient has currently been treated with systemic corticosteroid (deflazacort 5 mg/kg/die).

- 6) Boy, born preterm, affected by a “Cyrano hemangioma” : this patient was firstly treated with systemic corticosteroid (deflazacort 3 mg/kg/die) for 40 days; propranolol was started at the age of 9 months until 11 months, with improvement of the deep component but with an unaesthetic telangiectasic residuum. “Cyrano hemangioma” identified an IH localized at the tip of the nose which could lead to unaesthetic deformities. In agreement with the literature, it usually shows poor response to propranolol therapy. In our patient, a flat unaesthetic lesion persisted after systemic propranolol administration, so he was treated with topical propranolol (galenic formulation propranolol 1% cream) for 3 months looking forward to a potential future laser treatment.

Propranolol treatment was early stopped in 4 of 58 patients because of the onset of the following side effects:

1) Behaviour modification with irritability, sleep disturbances and neurological tics appeared in a 9-month-old girl, born at term, affected by 2 IHs, localized in the nose and in the thorax. Neurological evaluation excluded the propranolol involvement in the tics, however propranolol was stopped and the neurological tics spontaneously disappeared.

2) Hypoglycemia appeared in a girl, born at term, affected by a submandibular IH. The treatment was stopped after 2 months of therapy because of a hypoglycemic episode. Nevertheless, IH continued to spontaneously regress. Beta blockers may reduce gluconeogenesis, glycogenolysis and lipolysis increasing the risks of hypoglycemic episodes. Moreover, they may hide the signs of hypoglycemia. Hypoglycemia is more frequent when propranolol is administered in premature children at high dosage: our girl was 24 months old when propranolol was started as a delayed treatment of a submandibular hemangioma at the standard dosage

of 2 mg/kg/die. She had an episode of high temperature and convulsion with hypoglycemia.

3) Asmatiform bronchitic episodes appeared in a girl, born at term, affected by an ulcerated lip IH, during the propranolol treatment. The first episode needed the temporary stop of the therapy, then propranolol was reintroduced, but only after 1 month a similar second episode occurred. This episode required systemic steroids and antibiotics therapy so propranolol treatment was definitely stopped. The patient started application of topical beta blocker with good results.

4) Unspecified side effects referred by parents after only 2 days of therapy: parents decided to immediately stop the therapy. This patient was a preterm girl, affected by an abdominal IH, who started propranolol at 5 months of age.

Nineteen patients are currently under treatment: all of them show a good response to the therapy; in this group no side effects have been observed until now. Two of these patients have been treated for the second time with propranolol because of the recurrences occurred after stopping the first cycle. These 2 patients showed recurrences 5 and 12 months after therapy cessation.

Despite the good results, a large part of patients showed residual changes after the discontinuation of the propranolol therapy. However these changes were mild and no further systemic therapy was required.

Although topical beta blockers application is an off-label therapy, considering the encouraging literature data, we decided to prescribe this treatment to some patients. In our outpatients' clinic, some telangiectasic residuum of mixed hemangiomas previously treated with systemic propranolol, have been successfully treated with topical propranolol. Some patients were treated after the systemic propranolol therapy to reduce the

residual teleangiectasic vessels, others were treated before the systemic therapy in order to avoid or to procrastinate the last one.

Of the 78 patients treated with systemic propranolol, 9 patients received an additional topical beta blockers therapy. Eight patients applied topical beta blockers after systemic propranolol therapy in order to improve the aesthetic outcome and to reduce the risks of rebound of growth, whereas 1 patient applied timolol maleate solution before the start of the systemic therapy. Despite the application of topical timolol solution after the systemic therapy, one patient showed recurrence of the lesion and needed a second systemic propranolol administration. The duration of topical treatment depended on the response and varied from patient to patient.

Further 46 children (35 females, 11 males), affected by superficial IHs who did not require any other systemic therapies, were treated using topical beta blockers in order to improve the aesthetic outcome. All of them showed a good response without any side effects.

In summary, considering the whole group of our patients, (78 patients, 57 females and 21 males), we can establish that at the beginning of the therapy the mean age was 6 months; the mean period of propranolol treatment was 7,6 months.

58/78 patients completed the therapy: 47 with a good response (81%) (but 2 relapses and 3 early suspension for side effects)

6/58 (10,3%) patients showed recurrences which needed further systemic therapy

6/58 (10,3%) patients did not respond to the therapy

4/58 (6,9%) patients showed side effects and early stopped the therapy

9/78 (11,5%) patients received further topical beta blocker therapy

19/78 (100%) patients are still undergoing the therapy with a good response

1/78 (1,3%) patient was lost at follow up

Data of patients:

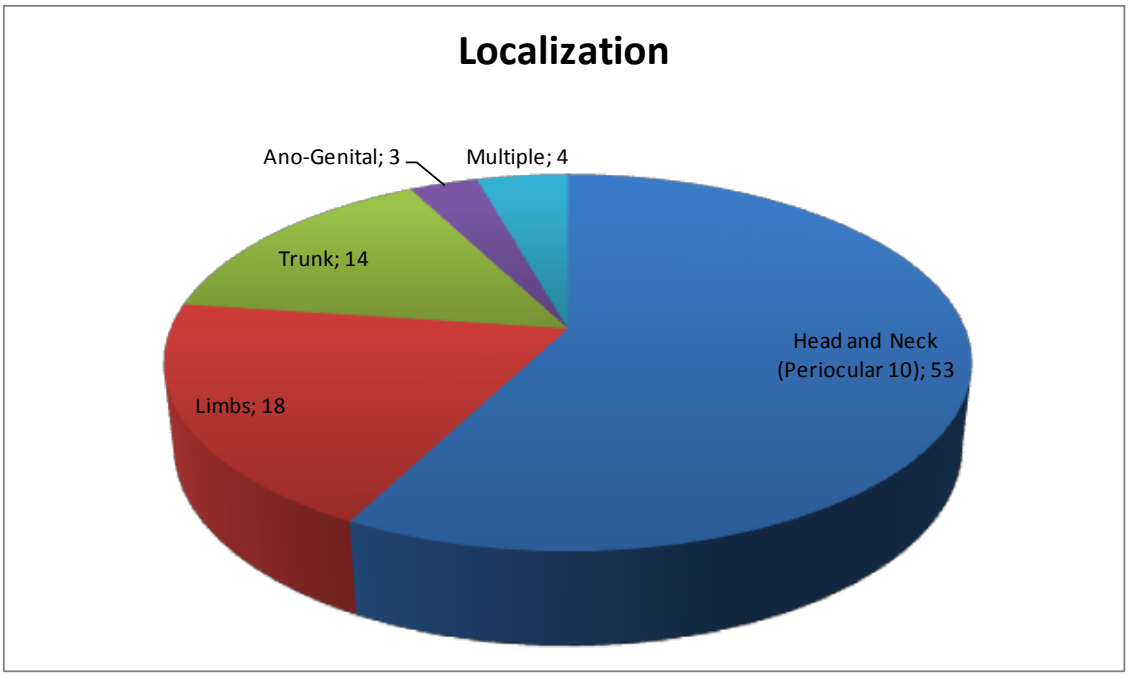
30/78 (38,5%) patients are preterm babies

6/78 (7,7%) patients are twins

20/78 (25,6%) patients whose mothers underwent instrumental diagnostic examinations during gestations (amniocentesis and chorionic villous sampling)

IHs Localization: (total number of IHs, considering that 11 patients showed more than one hemangioma)

- 53 IHs localized in the head and neck region: 10 periocular region, 3 beard hemangiomas with airways involvement
- 18 in the extremities
- 14 in the trunk
- 3 in the ano-genital region
- 4 patients had multiple hemangiomas: 2 with internal involvement, 1 of these is affected by hemangiomatosis
- 11 patients showed more than one IHs
- 9 patients showed segmental hemangiomas: 6 head and neck, 2 limbs, 1 lumbo-sacral (without internal involvement)


Localization
Ano-Genital; 3
Multiple; 4
Trunk; 14
Head and Neck
(Periocular 10); 53
Limbs; 18

7. CONCLUSIONS

In our experience, systemic propranolol at dosage of 2 mg/kg/day is an effective and safe treatment for IHs. Even if it is an off-label therapy, because it is still not approved for the IHs treatment, we consider it as the first choice for this kind of pathology. In fact, all the traditional therapies show less efficacy and more risks and side effects.

We would like to underline the necessity of a multidisciplinary approach when rare and complex IHs need to be treated. A team of physicians is necessary to adequately treat these patients and to follow them up, especially because of their very young age.

We tried to give some guidelines for the treatment of IHs: in fact, we provided a treatment protocol for complex IHs with a multidisciplinary approach to the patient recruitment and follow-up. It indicates dosage, monitoring and management of side effects, minimum duration of the treatment (at least until the end of the era of proliferation around the first year of life of the patient), treatment of relapses, management of non-responder patients and any aesthetic results once the therapy was completed.

In agreement with the literature, we observed greater risks of IHs in females than in males, in preterm babies and when amniocentesis or chorionic villous sampling were performed during gestation. Main localization is the head and neck region, followed by the extremities and the trunk.

Younger patients showed more benefits from propranolol therapy than older ones after the post-proliferative phase. However, some older patients received the treatment as first line-therapy with good clinical

improvement. So we confirm the opportunity of propranolol administration even if the proliferative phase is completed.

The mechanisms of propranolol-induced regression of IHs are not fully understood yet, but progresses have been made and in the future they will be better explained. However, we noticed the early effect that propranolol has on IHs due to vasoconstriction which is already evident in the first 48 hours; then we observed the intermediate and late effects which allow to induce and stabilize the regression of the IHs. We remarked an important difference in the various IHs we treated, both in the speed of response to propranolol and in the extent of the regression obtained, besides in the maintenance of the results at the end of therapy. According to the literature, we believe that there is a marked variability not only clinical but also in the behavior of IHs; this factor may explain why not all IHs, regardless of the type and location, respond in the same way, at the same rate, with the same risk of recurrences and long-term results.

Some IHs show a certain resistance to the therapy, regardless of the period of life when the administration starts and the therapy is completed.

This hypothetical resistance may be the cause of the non-responder patients and of the relapses which occur even when the treatment is completed in its post-proliferative phase and do not fully respond to the readministration of the drug.

In our cases relapses are not attributable to an early treatment withdrawal, except in one patient. They are likely to be due to the intrinsic characteristics of these IHs, that act as "exceptions".

In some cases recurrences may indicate that the proliferative phase of the IHs is probably still ongoing and that some IHs have a late proliferative phase. However, it is very difficult to predict which IHs will show this behavior. The exact mechanism underlying the late proliferative phase is

unknown: apoptosis of the endothelial cells is the best mechanism involved in the natural involution of IHs and propranolol is known to induce apoptosis. However, in some cases apoptosis could be not completed after propranolol withdrawal. The VEGF expression is involved in the proliferative phase of IHs and propranolol inhibits endothelial proliferation, antagonizing the VEGF receptors at the same time: probably these receptors are also involved in the recurrences after propranolol stop.

With regard to the side effects we observed, they were mild, in line with the data provided by the literature and they disappeared when the drug was stopped.

Even in patients in follow-up for more than one year after the end of the therapy (19/58 patients, 32.8%) we found no side effects related to the previous therapy with propranolol. Our experience allows us to confirm that the treatment with propranolol is well tolerated and with a good safety profile.

Further comparative studies are needed to determine the most effective dosage and the optimum duration of the treatment as well as large long-term studies in order to understand the risk of late adverse events.

Some patients received topical beta blockers to improve the aesthetic outcome: in our experience topical beta blockers therapy is effective and safe; no systemic and localized side effects have been recorded until now. Obviously a longer follow up period and a larger number of treated patients are necessary to draw interesting conclusions about the efficacy, the tolerability and the duration of the topical therapy.

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Table 1. LITERATURE REVIEW

Author	Country of study	Number of patients	Dose range (mg/kg d)	Age range (median, months) at initiation (months)	Duration of treatment (months)	Side effects	Outcome
Sans et al. 2009	France	32 total: 27 early intervention; 5 late	2-3 mg/kg/day	Mean 4,2 Mean 31	Mean 6,1	1 case mild hypotension;1 case wheezing	Good
Qin et al. 2009	China	58	1-1,5 mg/kg/day	Mean 4	Mean 3,5	37 cases diarrhoea; 18 cases sleep disturbances; 58 cases mild bradycardia	Good except 1
Manunza et al. 2010	United Kingdom	30	2 mg/kg/day	Mean 5,8	Mean 9,2	Not reported	Good
Buckmiller et al. 2010	USA	41	2 mg/dg/day	Mean 7,1	Not reported	6 cases sleep disturbances;2cases gastro-esophageal reflux;1case allergic reaction;1case respiratory syncytial virus exacerbation	16 good, 15 partial, 1 non-responder
Leboulanger et al. 2010	Multicentric: France	14 all airways	2-3 mg/kg/day	Mean 5,2	Mean 6	1case severe asthma	Good, 4 recurrences
Hogeling et	Australia	19	2	Mean 14	Mean 6	4 cases mild sleep disturbances;1 case dental	Good except 2

al. 2011			mg/kg/day			caries;4cases bronchiolitis	
Schiestl et al. 2011	Switzerland	25	2 mg/kg/day	Mean 3,6	Mean 10,5	4 cases mild transient bradicardia;6cases mild transient hypotension;3cases mild sleep disturbances	Good, 2 recurrences
Holmes et al. 2011	United Kingdom	31	3 mg/kg/day	Mean 3,9	Mean 3	1 case mild transient hypotension; 1case gastro-esophageal reflux (not surely related to propranolol)	Good except 4; 6 recurrences
Zaher et al. 2011	Egypt	30	2 mg/kg/day	Mean 6	Mean 7	None	18 Good; 6 partial; 5 poor; 1 non-responder; 5 recurrences
Babazgoitia et al. 2011	Multicentric: Argentina, Spain	71	1-2 mg/kg/day	Mean 5,8	Mean 3	10 cases mild sleep disturbances	Good except 1
Katona et al. 2012	Hungary	22	2 mg/kg/day	Mean 3,7	Mean 7	none	17 Good, 4 fair, 1 non-responder
Zvulunov et al. 2011	Multicentric: Israel, Canada, USA, Australia	42	2,1 mg/kg/day	Mean 28: beyond the proliferative phase	Mean 3,6	3cases mild sleep disturbances;1 case transient dyspnea	All good, none completely involuted

Shupp et al. 2011	Germany	55	2 mg/kg/day	Mean 6	Mean 5,8	13 cases mild side effects: cold extremities, dry skin, fatigue, gastrointestinal problems;1case bronchial asthma: early withdrawal of therapy	8 complete regression, 46 partial regression, 1 non-responder.
Gan et al. 2012	China	109	2 mg/kg/day	Mean: not clearly reported	From 6 to 12	23 cases mild side effects: hypotension, sleep disturbances, cold extremities, bronchitis, dry skin and gastrointestinal problems.	19 complete regression, 89 partial regression, 1 non-responder
Hermans et al. 2012	Netherland	174	2-2,5 mg/kg/day	Mean 4,8	Mean 10,7	108 cases mild side effects: 15 cases needed a dose reduction, 1case early discontinuation. Hypotension, wheezing, sleep disturbances, cold acra	173 good. 1 early discontinued and was treated with corticosteroid

Table 2. PATIENTS FROM OUR EXPERIENCE

PATIENTS UNDERGOING THE THERAPY					
Patient	***1***	***2***	***3***	***4***	***5***
Sex	Male	Male	Male	Male	Male
Birth	Preterm	At term	At term	Preterm	Preterm
IH Localization	Back	Cheek	Nose	Back	Nose (Cyrano), Gluteus, Foot
Internal IH	—	—	—	—	—
Age at onset	—	—	—	At birth	—
Age at onset of the therapy with Propranolol	6-months-old	4-months-old	13-months-old	9-months-old	2-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	Topical Beta Blocker for 7 months	—	—
Period of the therapy with propranolol	8 months	9 months	3 months	4 months	4 months
IH Response	Good after 2 months	Good after 4 months	Good	Good	—
Recurrences	—	Yes, 5 months after suspension, despite application of Topical Beta Blocker	—	—	—
Further cycle with Propranolol	—	Yes, still in therapy	—	—	—
Another therapy	—	—	—	—	—
Events during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	—	—	Amniocentesis	Chorionic Villous Sampling

Patient	***6***	***7***	***8***	***9***	***10***
Sex	Male	Female	Female	Female	Female
Birth	At term	At term	Preterm	At term	At term
IH Localization	Back	Multiple	Scalp and auricle	Eyelid and front	Submandibular
Internal IH	—	Hepatic and cerebral	—	—	—
Age at onset	3/4-weeks-old	—	—	At birth	3-months-old
Age at onset of the therapy with Propranolol	4-months-old	6-weeks-old	6-weeks-old	3-months-old	9-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	4 months	9 months	6 months	9 months	7 months
IH Response	Good	Good	Good	Good	Good, therapy just completed
Recurrences	—	—	—	Tendency to recur with gradual reduction of the drug (1 mg/kg/day), now employed full-dosage	—
Further cycle with Propranolol	—	—	—	—	—
Another therapy	—	—	—	—	—
Events during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	—	—	—	—

Patient	***11***	***12***	***13***	***14***	***15***
Sex	Female	Female	Female	Female	Female
Birth	At term	At term	At term	At term	At term
IH Localization	Beard H.	Scalp and scapula	Scalp and breast	Multiple superficial	Parotid
Internal IH	Airways	—	—	—	
Age at onset	—	—	At birth	At birth	1/2-months-old
Age at onset of the therapy with Propranolol	2-months-old	11-months-old	5-months-old	12-months-old	1-months-old
Dosage	2 mg/kg/day	1 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	6 months	7 months	7 months	9 months	7 months
IH Response	Good	Good	Good	Good	Good
Recurrences	—	—	—	—	—
Further cycle with Propranolol	—	—	—	—	—
Another therapy	—	—	—	—	—
Events during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	—	—	—	Amniocentesis

Patient	***16***	***17***	***18***	***19***
Sex	Male	Male	Female	Female
Birth	At term	Preterm	At term	At term
IH Localization	Jugular	Arm with ulceration	Gluteus, nose and abdomen	Glabella
Internal IH	—	—	—	—
Age at onset	—	—	—	2-months-old
Age at onset of the therapy with Propranolol	8-months-old	7-months-old	4-months-old	6-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—
Period of the therapy with propranolol	7 months	4 months	4 months	4 months
IH Response	Good	Good	Good	Good
Recurrences	—	—	Regrowth without therapy after 1 year	—
Further cycle with Propranolol	—	—	3 months, still in therapy	—
Another therapy	—	—	—	—
Events during the therapy	—	—	—	—
Side effects	—	—	—	—
Early conclusion of the therapy	—	—	—	—
Instrumental texts in the pregnant mother	—	—	—	—

PATIENTS WHO COMPLETED THE THERAPY					
Patient	***20***	***21***	***22***	***23***	***24***
Sex	Male	Male	Male	Male	Male
Birth	Preterm	At term	At term	Preterm	At term
IH Localization	Conjunctiva, Side and Foot	Temporo-parietal area and Shoulder	Multiple	Facial segmental with palpebral involvement	Palpebra
Internal IH	—	—	Liver	—	—
Age at onset	—	—	—	—	—
Age at onset of the therapy with Propranolol	4-months-old	4-months-old	2-months-old	4-months-old	4-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day then 3 mg/kg/day due to poor response	1,3 mg/kg/day for 1 month, then 2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	11 months	4 months	9 months	8 months	7 months
Age at the end of the therapy with Propranolol	15-months-old	8-months-old	11-months-old	12-months-old	11-months-old
IH Response	Good	Good	Good: slight increase of superficial telangiectasias	Poor	Good
Recurrences	—	—	—	—	—
Further cycle with Propranolol	—	—	—	—	—
Another therapy	—	—	Topical Beta Blocker	Systemic Corticosteroid	—
Time of the follow up after therapy suspension	6 months	1 year	3 months	1 month	14 months
Illness during the therapy	—	—	Viral exanthema: during this period (2 weeks) propranolol was stopped then reintroduced	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	Chorionic Villous Sampling	Chorionic Villous Sampling	—	Chorionic Villous Sampling

Patient	***25***	***26***	***27***	***28***	***29***
Sex	Female	Female	Female	Female	Female
Birth	Preterm, Twin	Preterm	Preterm, Congenital CMV at 24 weeks of pregnancy	At term	At term
IH Localization	Shoulder	Multiple	Arm with ulceration	Chest and Nose	Back
Internal IH	—	—	—	—	—
Age at onset	—	At birth	3-days-old	—	—
Age at onset of the therapy with Propranolol	10-months-old	3-months-old	7-months-old	5-months-old	7-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day then 5 mg/kg/day due to poor response	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	7 months	11 months	6 months	4 months	7 months
Age at the end of the therapy with Propranolol	17-months-old	14-months-old	14-months-old	9-months-old	14-months-old
IH Response	Good	Good	Absent	Good	Good
Recurrences	—	—	—	—	Slight regrowth
Further cycle with Propranolol	—	—	—	—	—
Another therapy	—	—	Surgery	—	—
Time of the follow up after therapy suspension	—	1 month	1 month	2 months	1 year
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	Sleep-wake irritability and physical TICS (anyway attributable to stress)	—
Early conclusion of the therapy	—	—	—	Because of the side effects	—
Instrumental texts in the pregnant mother	Chorionic Villous Sampling	—	Amniocentesis	—	—

Patient	***30***	***31***	***32***	***33***	***34***
Sex	Female	Female	Female	Female	Female
Birth	At term	Preterm	Preterm	At term	Preterm
IH Localization	Nose	Nose (Cyrano)	Front	Vulva	Abdomen
Internal IH	—	—	—	—	—
Age at onset	1/2-months-old	—	—	—	—
Age at onset of the therapy with Propranolol	4-months-old	5-months-old	3-months-old	4-months-old	5-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	4 months	7 months	9 months	9 months	2 days
Age at the end of the therapy with Propranolol	8-months-old	12-months-old	12-months-old	13-months-old	—
IH Response	Excellent	Good	Good	Good	Spontaneous regression when she was 1 year old
Recurrences	—	Slight regrowth without therapy after 3 months	—	—	—
Further cycle with Propranolol	—	—	—	—	—
Another therapy	—	Topical Beta Blocker (good response after 2 months)	Topical Beta Blocker	—	—
Time of the follow up after therapy suspension	3 months	6 months	7 months	9 months	6 months
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	—	Poorly tolerated
Early conclusion of the therapy	—	—	—	—	Unspecific side effects
Instrumental texts in the pregnant mother	—	Chorionic Villous Sampling	Amniocentesis	—	—

Patient	***35***	***36***	***37***	***38***	***39***
Sex	Female	Female	Female	Female	Female
Birth	At term	At term	Preterm	Preterm	Preterm
IH Localization	Lip	Abdomen	Occipite	Retroauricular	Thigh
Internal IH	—	—	—	—	—
Age at onset	At Birth	—	—	4/5-days-old	—
Age at onset of the therapy with Propranolol	2-months-old	4-months-old	12-months-old	3-months-old	4-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	7 months	10 months	7 months	9 months	6 months
Age at the end of the therapy with Propranolol	9-months-old	14-months-old	19-months-old	12-months-old	10-months-old
IH Response	Good	Good	Good	Excellent	Excellent
Recurrences	—	—	—	—	—
Further cycle with Propranolol	—	—	—	—	—
Another therapy	Topical Beta Blocker due to thin vessels	Topical Beta Blocker	—	—	—
Time of the follow up after therapy suspension	9 months	5 months	1 month	4 months	10 months
Illness during the therapy	2 episodes of asmatiform bronchitis during the last month of therapy. Initially propranolol was temporarily interrupted, then definitively stopped	—	—	—	—
Side effects	Asmatiform bronchitis	—	—	—	—
Early conclusion of the therapy	Yes, when she was 9 months old. Then topical beta blocker was applied	—	—	—	—
Instrumental texts in the pregnant mother	—	—	—	Amniocentesis	—

Patient	***40***	***41***	***42***	***43***	***44***
Sex	Female	Female	Female	Female	Female
Birth	Preterm	At term	At term	At term	At term
IH Localization	Lip	Arm	Shoulder	Submandibular	Parotid
Internal IH	—	—	—	—	—
Age at onset	—	—	—	—	—
Age at onset of the therapy with Propranolol	4-months-old	11-months-old	9-months-old	24-months-old (late start)	10-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	5 months	4 months	6 months	2 months	—
Age at the end of the therapy with Propranolol	9-months-old	15-months-old	15-months-old	26-months-old	—
IH Response	Good	Good	Good	Stable regression after 6 months	—
Recurrences	—	Slight recurrence after 3 months	—	—	—
Further cycle with Propranolol	—	—	—	—	—
Another therapy	—	—	—	—	—
Time of the follow up after therapy suspension	4 months	3 months	2 months	6 months	Lost at follow up
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	Hypoglycaemic episode	—
Early conclusion of the therapy	—	—	—	After hypoglycaemic episode	—
Instrumental texts in the pregnant mother	—	—	—	—	—

Patient	***45***	***46***	***47***	***48***	***49***
Sex	Female	Female	Female	Female	Female
Birth	At term	Preterm	Preterm	Preterm	At term
IH Localization	Chest and mandibular angle	Temporal paraheadset	Parietal with ulceration	Cheek	Lip with ulceration
Internal IH	—	—	—	—	—
Age at onset	Chest: at birth Mandibular: 1-week-old	At birth	At birth	At birth	At birth
Age at the onset of the therapy with Propranolol	12-months-old	14-months-old	6-months-old	9-months-old	21-months-old
Dosage	2 mg/kg/day	7,5 mg/kg/day	2 mg/kg/day	From 2 to 4 mg/kg/day	3 mg/kg/day
Previous therapies	—	—	—	Systemic corticosteroid for 6 months	Systemic corticosteroid for 3 months
Period of the therapy with Propranolol	4 months	3 months	5 months	10 months	7 months
Age at the end of the therapy with Propranolol	16-months-old	17-months-old	11-months-old	20-months-old	28-months-old
IH Response	Good	Good	Poor, lesion unchanged	Good	Poor
Recurrences	—	Slight recurrence after 2 months, but no therapy was performed	—	Regrowth at the suspension of the therapy	—
Further cycle with Propranolol	—	—	—	3 months	—
Another therapy	Surgery for aesthetic reasons	—	Surgery	Surgery after 2 months from the second cycle	Consulting maxillofacial surgeon
Time of the follow up after therapy suspension	15 months	1 year	10 months	2 months, then surgery	1 month, then surgery
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	Amniocentesis	Amniocentesis	—	—

Patient	***50***	***51***	***52***	***53***	***54***
Sex	Female	Female	Female	Female	Female
Birth	At term	At term	At term	At term	Post term
IH Localization	Lateral cervical region	Lip with ulceration	Segmental Arm	Zygomatic region and partial cheek	Telangiectatic ano-genital area and gluteus, with ulceration
Internal IH	—	—	—	—	—
Age at onset	Perinatal	At birth	At birth	1-month-old	At birth
Age at the onset of the therapy with Propranolol	10-months-old	4-months-old	8-months-old	4-months-old	3-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	—
Period of the therapy with propranolol	5 months	6 months	6 months	10 months	10 months
Age at the end of the therapy with Propranolol	15-months-old	11-months-old	14-months-old	14-months-old	13-months-old
IH Response	Good, but after 1 month the lesion relapsed	Good, further regression after the end of therapy	Good	Good	Good
Recurrences	After 1 month	—	—	—	—
Further cycle with Propranolol	Yes, started after 1 month and prolonged for 5 months, until the age of 21 months, with good results	—	—		—
Another therapy	Surgical consultation for aesthetic improvement	—	Topical steroid and Laser for atrophic skin and telangiectasias	—	—
Time of the follow up after therapy suspension	17 months	11 months	2 years and 6 months	7 months	2 years
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	Chorionic Villous Sampling	—	—	—	—

Patient	***55***	***56***	***57***	***58***	***59***
Sex	Female	Female	Female	Female	Male
Birth	At term	At term	At term	At term	Preterm, Twin
IH Localization	Parietal region and periorbital	Mucous lip, cheek, back, shoulder	Segmental reticulated lip, nose	Segmental hemi-face and leg	Nose (Cyrano)
Internal IH	—	—	—	—	—
Age at onset	At birth	At birth	1-week-old	At birth	At birth
Age at the onset of the therapy with Propranolol	6-months-old	5-months-old	6 weeks old	2-months-old	8-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	3 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	—	—	Systemic corticosteroid for forty days
Period of the therapy with propranolol	10 months	10 months	7 months	9 months	2 months
Age of end therapy with Propranolol	16-months-old	15-months-old	8 months and 2 weeks old	11-months-old	11-months-old
IH Response	Good	Good	Good	Good	Poor
Recurrences	—	—	—	—	—
Further cycle with Propranolol	—	—	—		—
Another therapy	Topical Beta Blocker	—	—	Laser treatment for aesthetic reasons after 9 months	Topical Beta Blocker for 3 months
Time of the follow up after therapy suspension	7 months	2 years	2 years	1 year	9 months
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	—	Chorionic Villous Sampling	—	—

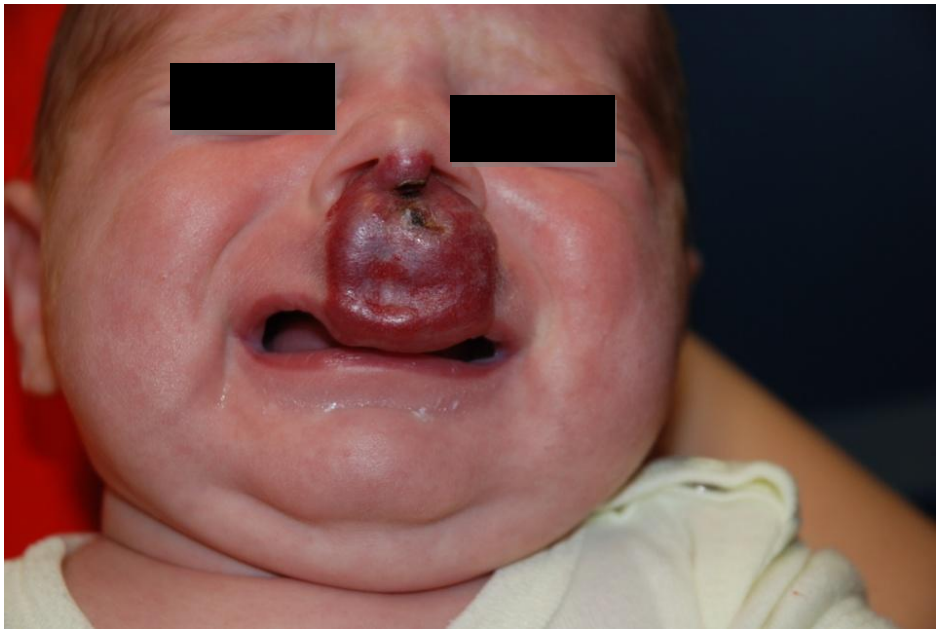
Patient	***60***	***61***	***62***	***63***	***64***
Sex	Male	Male	Male	Female	Female
Birth	At term	Preterm, Twin	At term	Preterm	Preterm
IH Localization	Lip and vestibule of the nose	Eyelid	Deep periorbital	Forearm and third finger	Inferior lip with mucous involvement
Internal IH	—	—	—	—	—
Age at onset	1-week-old	At birth	At Birth	10-days-old	2-months-old
Age at the onset of the therapy with Propranolol	6-months-old	9-months-old	4 years old	5-months-old	5-months-old
Dosage	3 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	Systemic corticosteroid for 4 months and 10 days	Topical corticosteroid	—	—	—
Period of the therapy with propranolol	2 months	8 months	2 months	8 months	6 months
Age of end therapy with Propranolol	8-months-old	17-months-old	4-years-old	13-months-old	11-months-old
IH Response	Good	Good	Absent	Good	Good
Recurrences	—	—	—	—	—
Further cycle with Propranolol	—	—	—		—
Another therapy	—	—	Surgical consultation	—	—
Time of the follow up after therapy suspension	9 months	2 years	2 years	10 months	1 year
Illness during the therapy	—	—	—	—	—
Side effects	—		—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	—	—	—	Chorionic Villous Sampling

Patient	***65***	***66***	***67***	***68***	***69***
Sex	Female	Female	Male	Female	Female
Birth	Preterm	At term	At term	At term	At term
IH Localization	Beard H with lip involvement	Front	Lip with ulceration	Beard H.	Subscapularis, shoulder, vulva
Internal IH	Airways	—	—	Airways and Parotid	—
Age at onset	At birth	At birth	At Birth	At birth	At birth
Age at the onset of the therapy with Propranolol	2-months-old	5-months-old	2-months-old	40-days-old	16-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 - 3,5 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	—	Topical and systemic antibiotic	—	—
Period of the therapy with propranolol	14 months	6 months	8 months	9 months	7 months
Age at the end of the therapy with Propranolol	16-months-old	11-months-old	10-months-old	10-months-old	23-months-old
IH Response	Good	Good	Good	Good	Good
Recurrences	After 3 months only for the lip IH, not for the airways	—	Regrowth at the first suspension of the therapy after 3 months and a second regrowth after 6 months from the second suspension of the therapy	—	—
Further cycle with Propranolol	For 3 months	—	A second one for 9 months with partial result and a third one for 10 months until he was 3 years and 2 months old with partial improvement		—
Another therapy	Surgery for lip IH after a second recurrence at a distance of 8 months	—	—	—	—
Time of the follow up after therapy suspension	8 months	8 months	4 months	2 years	1 year
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the pregnant mother	—	—	—	—	—

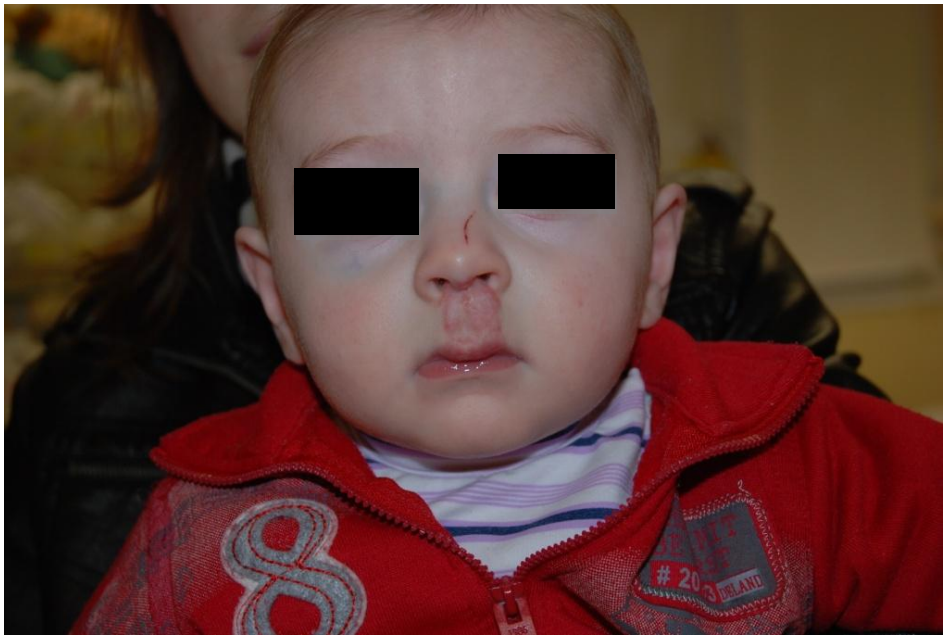
Patient	***70***	***71***	***72***	***73***	***74***
Sex	Female	Female	Female	Male	Male
Birth	Preterm	Preterm	At term	At term, Twin	Preterm, Twin
IH Localization	Side	Palpebra	Submandibular	Front	Periocular
Internal IH	—	—	—	—	—
Age at onset	Perinatal	Perinatal	3-months-old	1-month-old	At birth
Age at the onset of the therapy with Propranolol	7-months-old	1-month-old	5-months-old	6-months-old	2-months-old
Dosage	2 mg/kg/day	1,8 - 2 mg/kg/day	1 for 1 week then 2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	Metronidazol cream for ulceration	Systemic corticosteroid 3 gtt/kg	—	—	—
Period of the therapy with propranolol	11 months	13 months	9 months	11 months	11 months
Age at the end of the therapy with Propranolol	18-months-old	14-months-old	14-months-old	17-months-old	13-months-old
IH Response	Discreet	Discreet	Good	Good	Good
Recurrences	—	Regrowth at the first suspension of the therapy after 3 weeks and a second regrowth after 1 month from the second suspension of the therapy	Regrowth at the first suspension of the therapy after 9 months	—	—
Further cycle with Propranolol	—	A second one for 3 months and a third one for 3 months until she was 2 years and 2 months old	A second one for 6 months, actually still in regression		—
Another therapy	Indicated surgery for aesthetic improvement	Surgery for aesthetic improvement	—	—	—
Time of the follow up after therapy suspension	1 year	6 months	6 months	8 months	6 months
Illness during the therapy	—	—	—	—	—
Side effects	—	—	—	—	—
Early conclusion of the therapy	—	—	—	—	—
Instrumental texts in the mother	—	Amniocentesis	—	—	Amniocentesis and Chorionic Villous Sampling

Patient	***75***	***76***	***77***	***78***
Sex	Male	Female	Female	Female
Birth	At term	Preterm	At term	Preterm, Twin
IH Localization	Shoulder	Leg with ulceration	Segmental Arm	Palpebral region
Internal IH	—	—	—	—
Age at onset	At birth	At birth	At birth	At birth
Age at the onset of the therapy with Propranolol	9-months-old	4-months-old	3-months-old	2-months-old
Dosage	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day	2 mg/kg/day
Previous therapies	—	Topical antibiotic and Metronidazol gel for ulceration	—	—
Period of the therapy with propranolol	6 months	4 months	11 months	13 months
Age at the end of the therapy with Propranolol	15-months-old	8-months-old	14-months-old	15-months-old
IH Response	Good	Good	Good	Good but slow
Recurrences	—	—	—	—
Further cycle with Propranolol	—	—	—	
Another therapy	—	—	—	—
Time of the follow up after therapy suspension	1 year	3 months	1 year	6 months
Illness during the therapy	—	—	—	—
Side effects	—	—	—	—
Early conclusion of the therapy	—	—	—	—
Instrumental texts in the pregnant mother	—	Amniocentesis, Chorionic Villous Sampling	—	Amniocentesis

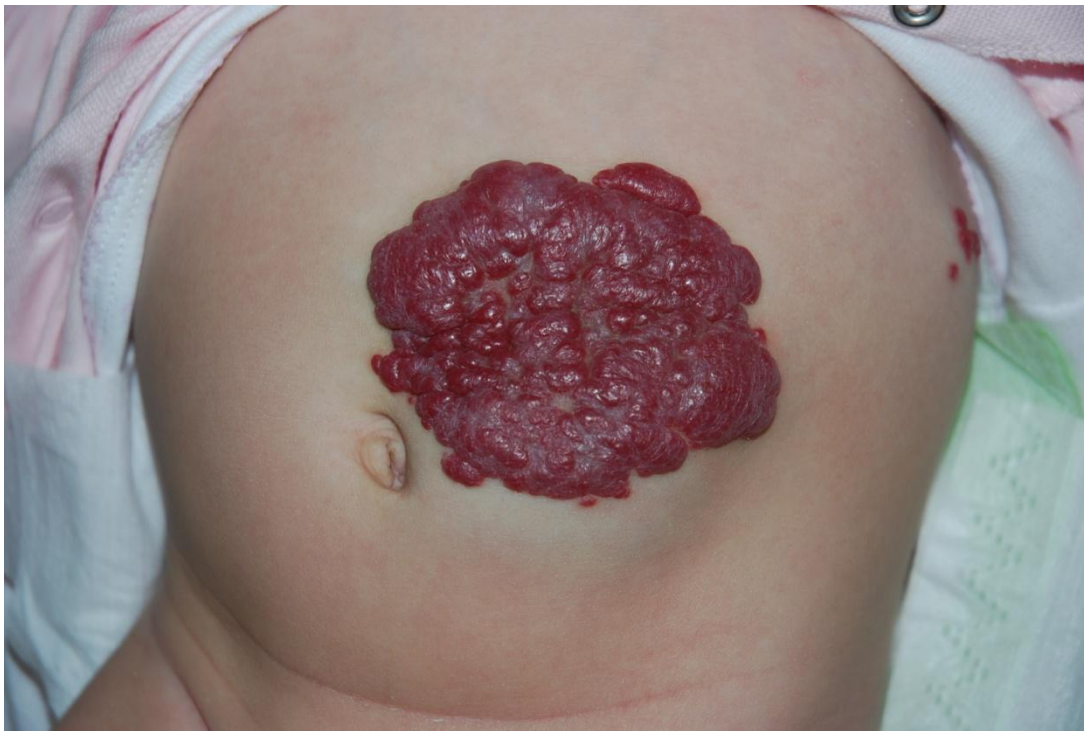
10. PICTURES



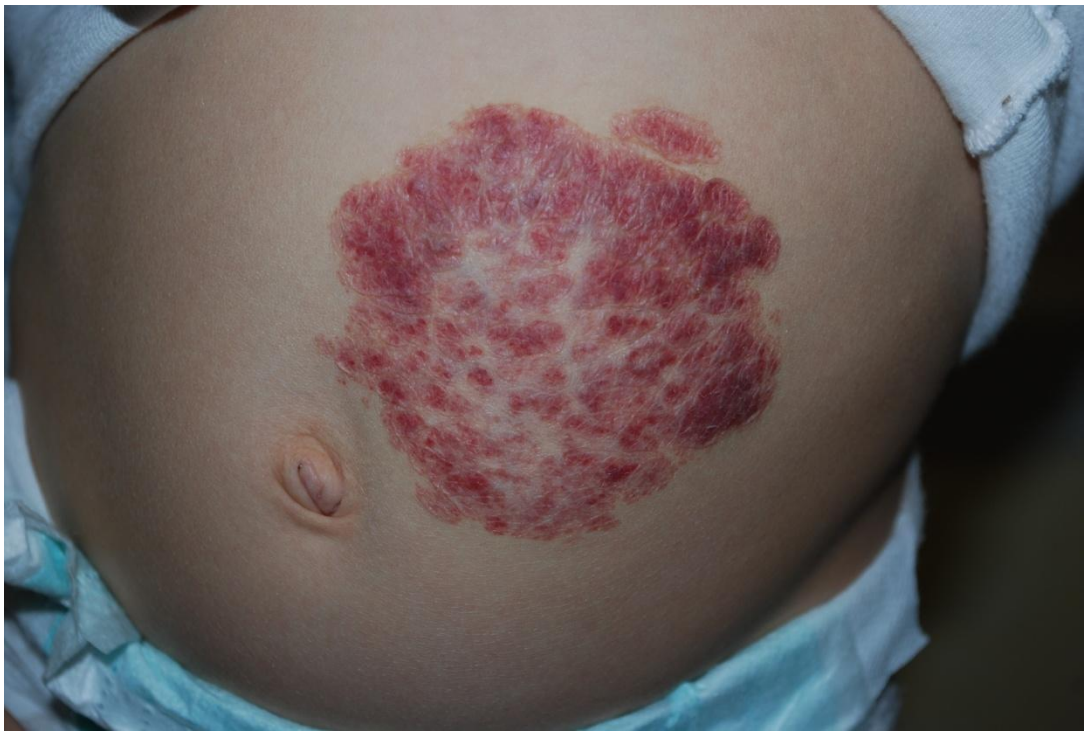
1) Girl at 2 months of age, affected by an ulcerated lip and nasal IH.



2) The same patient at 7 months of age, after 5 months of propranolol 2 mg/kg/day



3) 4-months-old girl, affected by a voluminous abdominal IH.



1) The same girl al 19 months of age, after 10 months of systemic propranolol 2 mg/kg/day and 4 months of topical beta blocker.