HAEMANGIOMAS OF THE ORBITAL REGION IN CHILDREN

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SUMMARY

The paper presents summary report which approaching the issue of this affection and includes a retrospective study aims to evaluate the effectiveness and safety of treatment modalitiesinfantilehemangiomasperiorbitalandorbitallocalizationin paediatric patients observed in the period 2009–2014 on the Children's Eye Clinic.

Key words: haemangiom, treatment modalities

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INTRODUCTION

Vascular lesions of the orbit cover tumours such as capillary and cavernous haemangiomas and haemangiopericytomas, as well as malformations such as lymphangiomas, orbital varices and arteriovenous malformations. Infantile haemangiomas rank among the most common tumours of the orbit and eyelids in children. Although observations about this vascular anomaly have been gathered over the course of the previous decades, the etiology and pathophysiology are not completely known. In recent years the approach to this pathology has changed by means of research endeavours and in particular with progress in the strategy of treatment.

Infantile haemangiomas are typical in their development. Rapid growth is followed by slow spontaneous involution. Despite its benign character, this pathology of the periorbital region may cause a deterioration of vision, strabismus, various deformities and may even endanger the life of the child.

The variability of the phenotype and actual manifestations of the pathology require an individual approach to treatment. Until recently the basis of treatment in the case of risk haemangiomas was glucocorticoids. Further possibilities are interferon alpha and vincristine, but these carry the risk of serious adverse effects. Surgical therapy and diode lasers are of assistance in therapy, however, their use is relatively limited in the case of larger scale problematic haemangiomas. Thanks to the chance discovery of the efficacy of beta-blockers published for the first time in 2008 (62), today they are becoming the medicament of first choice in the therapy of problematic infantile haemangiomas (11, 26, 40, 42, 79, 80, 97).

NOMENCLATURE

Although these lesions have been known for several centuries, they were first formally characterised by Lister (64), who referred to them colloquially as "strawberry naevi". These non-malignant vascular hamartomas have been given several names, including capillary haemangiomas, juvenile haemangiomas, haemangioblastomas, benign haemangioendotheliomas or hypertrophic haemangiomas. They are of mesenchymal origin and ensue from the endothelium of the blood vessels.

The historical lack of uniformity in the naming and classification of haemangiomas eventually required a more stringent categorisation, by which the present definition of infantile haemangioma originated as a unique vascular tumour which originates after birth in breastfeeding age and passes through a proliferative phase followed by spontaneous involution (50). However, infantile haemangiomas must not be confused with congenital haemangiomas, which are fully formed at birth.

Histopathologically a capillary haemangioma is an altogether well bordered, non-capsulated formation consisting of a ball of small capillaries covered by the endothelium. A cavernous haemangioma is formed by a system of larger vascular areas, separated by ligament septa. The microscopic structure is similar to the cavernous bodies of the genitals (68, 77).

EPIDEMIOLOGY

The incidence of infantile haemangioma of the orbit is stated at 3 to 10% in the literature (55). Recent reviews confirmed that the probable incidence is 4-5% (55). A large multicentric prospective study which examined the demography of infantile haemangioma found female sex, Caucasian ethnicity, premature birth with low birth weight, placental abnormalities, multiple pregnancies, advanced age of the mother and pre-eclampsia to be risk factors (39). A further potential risk factor is chorionic villus sampling. There is a racial predilection for white individuals (10-12%) in comparison with those of black origin (1.4%) and the

Taiwanese and Japanese population (0.2-1.7%) (39).

The area of the head and neck is the most frequently afflicted area (60%), followed by the torso (25%) and limbs (15%). Haemangiomas are often solitary, nevertheless up to 20% of children have multiple localisation. In addition to the skin they may occur also in the brain and visceral organs (3, 11, 12, 15, 25, 46).

CLINICAL SYMPTOMS

Infantile haemangiomas may appear at any time on the skin, but are most frequently located in the area of the head and neck (63). Capillary haemangiomas occur more frequently in females than males, within a ratio of 3:2, without manifest familiar heredity. Their incidence is increased in prematurely born children. Approximately one third of capillary haemangiomas are present from birth, and almost all are identified by the age of six months (38). Their clinical picture may differ markedly in localisation, size, depth and speed of growth. Lesions are divided into three main subtypes on the basis of depth of growth, namely into superficial, deep (subcutaneous) or a combination thereof. In the region of the orbit there is a predilection for localisation on the upper eyelid and upper section of the orbit. Superficial lesions appear as bright red papules or nodules, which may have a bumpy appearance. Deeper lesions cause variable changes in skin colouring, depending on their distance from the surface. Occasionally they may be of a blue or purple colouring, or have no colouring whatsoever.

The third subtype contains elements of both superficial and deep lesions. Whereas lesions are often classified according to the depth of growth, it has been demonstrated that morphological classification into localised (discrete) or segmental (incorporating broad anatomical areas) is indicative for the clinical course (45). The majority of lesions are localised (72%), while segmented and multifocal cover 18% and 3% respectively (46). On average their size is 0.5-5cm, but ranges from the size of a pin head to lesions larger than 20 cm in diameter.

Infantile haemangiomas differ from other vascular malformations of early childhood in their characteristic clinical course. Although each lesion may have a different growth model, the majority follow a typical course, divided into the following six stages: 1. “incipient” phase, 2. early proliferative phase, 3. late proliferative phase, 4. plateau, 5. involution, 6. death (36, 45, 48). The incipient phase is the stage before the emergence of the lesion and usually lasts for 0-3 months. During the course of the next 6-10 months the spread of the lesion passes through two stages, namely the early proliferative phase, characterised by rapid growth in the first months of life, in which lesions reach the majority of their final size. This is followed by the late proliferative phase, with less rapid growth. It generally applies that 80% of infantile haemangiomas reach their maximum size within 5 months. Superficial (localised) lesions have a slightly extended proliferative phase in comparison with deep (segmented) lesions, persisting for something over 6 months, but the majority of lesions cease to grow by the age of 9 months (45). The proliferative phase is followed by a plateau or stabilisation phase, with a variable period of duration. Involution is usually heralded by a change of colour from bright red to purple or grey, together with a softening of texture, flattening or reduction in size. Approximately one half of infantile haemangiomas involute by the age of four years, and three quarters by the age of seven (66).

Although the majority of infantile haemangiomas have an uncomplicated clinical course, some may cause substantial morbidity, requiring treatment. Amblyopia is the most common ocular complication, affecting 40-60% of patients (38, 83). Lesions in the periocular region with a size of more than 1 cm in their largest dimensions are generally predictive of blunt sightedness, and require treatment (88). The most common complication caused by affliction in the area of the eyelids indicating astigmatism is anisometric amblyopia, and in the case of occlusion of the optic axis this leads to deprivative blunt sightedness.

Orbital lesions are less common, but due to their size may have the secondary consequence of strabismus, protrusion, exposure keratopathy or pressure neuropathy of the optic nerve (38). The presence of any of these complications requires immediate intervention. 40-80% of infantile haemangiomas may leave permanent residues even after the tumour involutes (9, 43).

PATHOGENESIS

Although the precise pathogenesis of haemangiomas is not entirely clear, histopathological studies to date have improved our knowledge of this pathology. Several separate studies have examined genetic factors, which indicated that heredity does not play a large role. This is in accordance with the findings of sporadic incidence of infantile haemangiomas. However, other genetic studies speculate with regard to genetic distribution, which is attested to by the doubling of the risk for a family member of the proband (16), whilst the racial predilection for white individuals in comparison with “non-whites” also indicates a certain genetic component. Research into molecular markers presented by haemangioma cells, cultivated endothelial cells (HemEC) and haemangioma stem cells (Hem Sc) have shed light on possible mechanisms of origin. Angiogenesis (i.e. proliferation or migration from already existing blood vessels) and vasculogenesis (i.e. de novo formation of blood vessels from progenitor cells) apply in the pathogenesis of infantile haemangiomas (92). Further studies of the expression of samples of cultivated haemangioma cells (HemEC) determined up-regulation of glucose transporting protein type 1 (GLUT-1), vascular endothelial growth factor (VEGF), among other factors also down-regulation of other markers such as CD 146 (16, 50). GLUT-1 is especially useful in the diagnosis of those lesions that we may find exclusively in the case of infantile haemangioma (61). Attention is now turning to angioproliferative signalling molecules such as VEGF as a key molecule for the formation of blood vessels and a probable basis for the origin of infantile haemangioma. Raised levels of VEGF-A in serum have been recorded in patients with proliferative infantile haemangioma in comparison with haemangiomas in involution (99).

Similarly, stem cells isolated from a human infantile hae-

mangioma manifested expression of VEGF-A in the proliferative phase, but not in the phase of involution. This finding was further examined in the configuration of a selection of traditional therapeutic agents, namely corticosteroids. In vivo studies on mice demonstrated that dexamethasone blocked secretion of VEGF-A in stem cells derived from infantile haemangioma (34). Connected studies provide evidence of a possible mechanism in the relationship of steroid inhibition NF-κB, molecules associated with inflammation, as well as with angiogenesis (33). In addition to this it was demonstrated that HemEC is capable of forming functional blood vessels with a "haemangioma-like" phenotype without further mesenchymal support, which is required by other cell populations (54).

Research into the cellular origin of haematopoietic stem cells of infantile haemangioma points to a population of cells referred to as endothelial progenitor cells (EPC). This is documented by findings of increased EPC in peripheral blood in patients with infantile haemangioma, EPC associated markers localised on the endothelium of proliferating haemangiomas and markers linked with primitive haematopoietic cells located on forming capillaries of the endothelium (47). Nevertheless, previous studies imply a possible placental origin on the basis of cross-correlations of endothelial cells of haemangioma and placental cell markers (7, 73). Finally it is still necessary to take into consideration molecular pathogenesis, but recent progress, as described above, offers new targets for future therapy, primarily VEGF.

HISTOPATHOLOGY

The clinical course of infantile haemangioma is a reflection of histopathological changes. Early proliferating haemangiomas are composed of a cellular mass of compact premature capillaries lined with loose endothelial cells with high mitotic activity (71, 75, 89). In the later stage endothelial cells reduce in size, lesions are composed of several formed vascular structures lined with flat endothelial cells (99). In the stroma we find a large number of fertile cells and pericytes in the walls of the blood vessels. And finally, in the phase of involution, the mitotic activity of the cells progressively declines and the vascular tissue is replaced by fibrotic fat tissues, which leads to fibrosis and eventual atrophy (71).

DIAGNOSIS

The majority of superficial lesions are determined clinically. The diagnosis is generally evident according to the clinical course, colour and "whitening" after impression. In addition, infantile haemangiomas both increase in size and darken, whereas vascular formations generally do not change their colouring. If a lesion of an unusual appearance, growth tendency or other phenotype appears, there are a number of diagnostic procedures that may be used. The presence of bFGF (basic fibroblast growth factor) in urine is examined, as well as VEGF in serum as markers for infantile haemangioma (81, 99). In children with a proliferating haemangioma there is an increased level of bFGF, in vascular malformations the level is normal. In deep lesions imaging methods are used in order to support diagnosis, clarifying

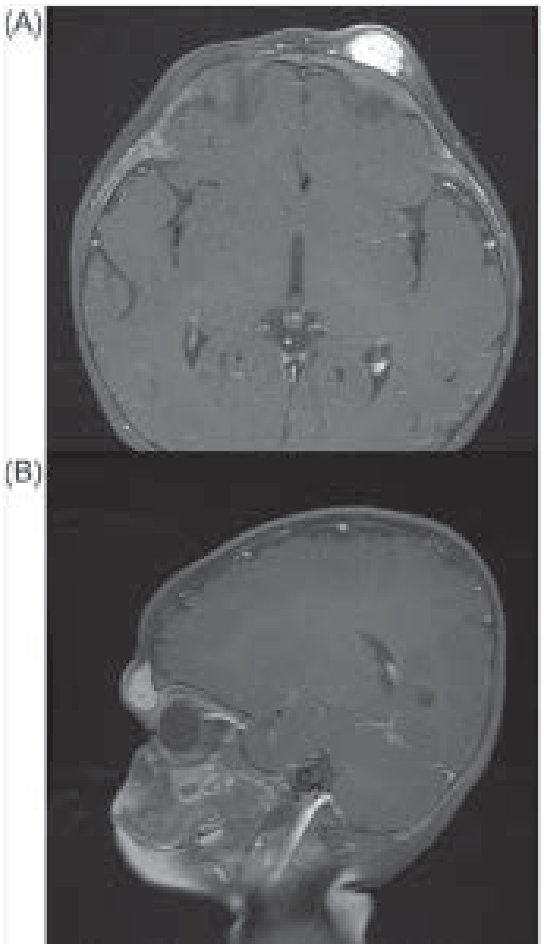

Fig. 1 Magnetic resonance imaging displaying in T1 post-contrast axial (A) and front-to-back (B) well bordered, clearly shining lesion of left forehead and upper eyelid
Source: Alison B., Callaha M.D., Michael K., Yoon M.D.: Infantile haemangiomas: A review

the size of the lesions. Ultrasonography shows increased density of blood vessels and increased through flow, but this modality has limitations in displaying the full scope of the lesion and the impact on the surrounding structures (18). Doppler ultrasound shows a high through-flow model.

Magnetic resonance with or without administration of gadolinium displays a well bordered formation, which is isointense with extraocular muscles in T1 display and hyperintense in T2. The image is accentuated with contrast (70). Even if MRI is generally more expensive and less available than computer tomography (CT), MRI diagnosis is recommended in order to prevent the exposure of children in this vulnerable age group to radiation. If CT is necessary the dose of radiation used should be commensurate with regard to age. On CT haemangiomas are displayed as a homogeneous mass with draining blood vessels, accentuating with contrast. In certain cases the use of CT or MRI angiography may be useful. It is necessary to emphasise that in lesions of unclear etiology, unusual appearance, orbital localisation or other atypical manifestations a biopsy may be performed, which will lead us to the final diagnosis. It is used in differential diagnostics incorporating lymphangio-

mas, rhabdomyosarcomas and metastasis of neuroblastomas in the orbit. GLUT-1 exprimated only via endothelial cells of haemangiomas may confirm the diagnosis.

DIFFERENTIAL DIAGNOSTICS

There are a number of vascular tumours which have a similar appearance to infantile haemangioma. Congenital haemangiomas are fully formed at birth, which differentiates them from infantile haemangiomas. One of the most common vascular malformations in the region of the head and neck in childhood age is the naevus flammeus or port-wine stain. These lesions may be connected with Sturge-Weber syndrome. They have a clinical appearance similar to infantile haemangiomas, but do not whiten after impression. They appear as a flat, sharply bordered macular lesion of the eyelids, cheeks and forehead with colouring from pink, via red to dark purple. Histopathologically we find a normal epidermis with abnormal plexus of dilated, thin-walled blood vessels in the dermis or subcutaneously. In childhood the surface is smooth, later nodular unevenness to hemihypertrophies of the face appear. In the region of the head, naevus flammeus formations are usually distributed in the innervation zones of the trigeminus, but frequently do not entirely copy them and exceed the central line.

Sturge-Weber syndrome (or encephalotrigeminal angiomatosis) is a phacomatosis afflicting the eyes, face and leptomeninges. Naevus flammeus is localised in the area of the first two branches of the nervus trigeminus. In the brain we may find leptomeningeal malformations, mostly parieto-occiptally ipsilaterally with the naevus. This is also connected with epileptic seizures, which are resistant to treatment. Contralateral hemiparesis and homonymous hemianopsia may also occur. Ophthalmological findings include unilateral diffuse choroidal haemangioma, less frequently haemangioma of the episclera, iris or ciliary body. In 30% of cases ipsilateral secondary glaucoma develops (2, 12, 51, 57, 74).

Kaposiform haemangioendotheliomas are rare vascular tumours which may be locally aggressive with regard to their rapid and massive growth tendency. They are usually already formed at birth, although they may also appear shortly afterwards. Therapy is aggressive in order to limit their destructive character. Angiomas are cutaneous or subcutaneous lesions, which are generally benign and characterised by slow growth. Kaposiform haemangioendotheliomas and angiomas may be linked to Kasabach-Meritt syndrome and the phenomenon of lamellar sequestration, which may have the consequence of severe, life-threatening coagulopathy (52). Vascular malformations differ from tumours in that they are conditioned by a defect of vascular development, have a non-proliferating endothelium and generally persist without regression.

Pyogenic granuloma belongs to the group of mesenchymal tumours in the periocular region, similar to infantile haemangioma. It is a relatively common, benign lesion of the skin and mucous membranes. In children and young adults it appears as a solitary, shiny red papule or nodule, susceptible to haemorrhage. It develops over the course of a few weeks, most frequently on the face, on the hirsute areas of the head and in the regions of the upper limbs. It probably originates in connection with a minor trauma (76).

Acquired tufted haemangioma is a rarer benign vascular tumour, characterised by clusters of blood vessels. It is typically manifested in infants or in early childhood as a solid tumour, or as more extensive flat formations of dark red to purple colouring, sensitive to painful upon palpation (10, 29).

It is necessary to exclude from afflictions of the orbit, which similarly to intraconally localised haemangiomas may cause protrusion of the bulb, such inborn abnormalities as congenital arteriovenous malformations, lymphangiomas or orbital cephalocele. Congenital AV malformation is characterised as soft, reducible resistance with slow progression. Lymphangioma is manifested in older children aged between 3-5 years and is characterised by infiltrative growth beneath the conjunctiva and into the hypodermis of the eyelids. Orbital cephalocele typically pulses, and there is a typical bone defect on RTG and CT. Haematocysts are a frequent cause of exophthalmos immediately after birth. They usually originate after a birth trauma, with spontaneous haemorrhage, and are reabsorbed within the course of a few weeks (4).

Primary benign tumours which may imitate deep infantile haemangiomas include dermoid and epidermoid cysts. They have a palpation finding of a stiff ligament capsule.

TREATMENT

The largest problem in managing the treatment of infantile haemangioma is the actual decision on its commencement. Many haemangiomas regress spontaneously, and intervention carries a risk, because the need to intervene is not always clear. The main aims of treatment are the prevention and reversal of a threat to life or function-endangering complication, prevention of permanent disablement, reduction of psycho-social stress for the patient and family and avoidance of aggressive or harmful interventions in the case of lesions which may have an excellent prognosis without treatment (24). The health consequences of intervention depend on the size and location of the lesion and the age of the patient. All these factors may be evaluated and the final decision for treatment should depend on the relative influence of each of them. Small lesions which do not jeopardise sight or other important functions can be merely observed in the initial phases. Nevertheless, even despite the self-limiting nature of the lesion, the potential consequences may require treatment. A feared and frequent complication in the case of periocular haemangiomas is amblyopia. It is necessary to intervene if strabismus, pseudoptosis or anisometropia are present (38, 83). Some lesions, especially those that are large and heavy, may lead to damage to the skin and surrounding structures and leave behind a scar, which remains even after the healing of the haemangioma. Very large or constantly enlarging lesions usually require intervention.

Steroids

In 1963 an effect on reducing the size of haemangiomas was demonstrated by chance in the treatment of thrombocytopaenia with systemic steroids (usual dose 2-5 mg/kg) (53). They represent the historical foundation of treatment. The mechanism of effects of corticosteroids is not yet completely known. Inhibition of expression of VEGF-A, with sub-

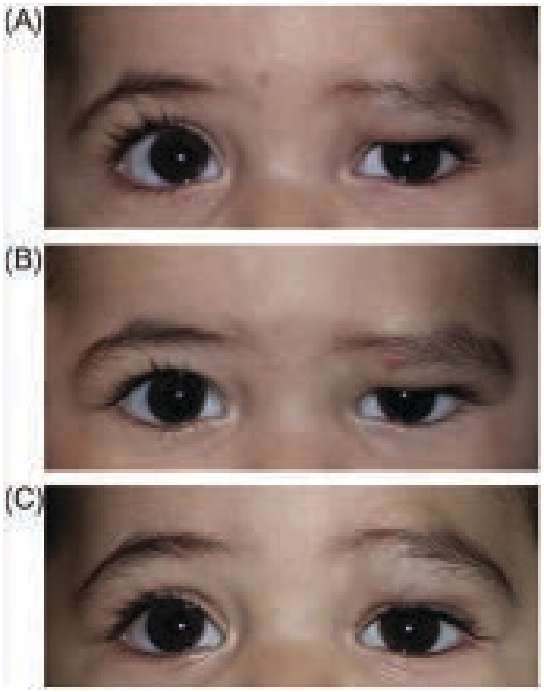

Fig. 2 Involution of haemangioma following intralesional steroid injection. (A) before commencement of treatment, (B) one week after injection, (C) 4 weeks later
Source: Alison B., Callahan M.D., Michael K., Yoon M.D.: Infantile

sequent inhibition of proliferation of germ cells was demonstrated on animal models. They increase vascular sensitivity and secondarily cause vasoconstriction. In more extensive studies, prednisone was administered in large doses (20 mg per day over a period of 3-8 weeks). These demonstrated a response level of 84% after two months of treatment. Others required up to six months of treatment. Nevertheless, this relatively high response rate is accompanied by a 35% level of incidence of adverse effects, including behavioural changes, Cushingoid appearance and delayed growth (8).

Corticosteroids should be applied in the proliferative phase, because they have only an imperceptible effect on stable or involuting haemangiomas.

Intralesional steroids

In an endeavour to reduce systemic side effects of peroral steroids, experiments began with locally applied steroid therapy. A mixture of betamethasone 6 mg/ml and triamcinolone 40 mg/ml in a ratio of 1:1 with a volume of 1 to 2 ml is injected intralesionally, depending on the size of the lesion. The response may be very rapid, with an improvement generally within a few days. Nevertheless, with regard to the direct communication between the lesion and the systemic vascular channel, periocular intralesional steroid injections carry a small but very real risk of embolisation of the arteria ophthalmica (59, 84, 87). Further local complications include cutaneous hypopigmentation, fat atrophy, calcification and necrosis of the eyelid (13, 17, 90, 95, 98). Although it occurs only rarely, following local use of steroids dysfunction of the adrenal glands may also result (98). Intralesional steroids are now overall the second line in the treatment of non-regressing lesions.

Local steroids

The use of local steroids began from the mid 1990s (14, 19). Although this method of treatment has far less serious systemic adverse side effects than intralesional steroids, it nevertheless brings with it the potential of side effects such as hypopigmentation, hypertrichosis, glaucoma, cataract, and if used for a longer period is effective only for superficial lesions.

Interferon alpha

Interferons are glycated proteins with antiproliferative, immunomodulating and antiviral activity. Interferon alpha is used in the oncological treatment of chronic myeloid leukaemia, trichocellular leukaemia, also for Kaposi's sarcoma in patients with AIDS etc.

Its pronounced inhibiting effect on angiogenesis is used also in the treatment of haemangiomas not responding to corticoids. The majority of interferons used today are prepared by the technology of recombinant DNA. Interferon alpha 2a and 2b is used in subcutaneous injections in a dose of 1-3 million units/m2 of body surface per day. In addition to neutropenia, adverse effects in connection with its use include potentially irreversible spastic diplegia. Despite its effectiveness, the risk of neurotoxicity is 10-30%, as a result of which its use in treatment has been discontinued (25).

Vincristine

Vincristine is a chemotherapeutic drug which induces apoptosis by binding to tubulin and disturbing the function of the spindle apparatus and thereby terminating mitosis. It is used within the framework of various combinations in the treatment of haematological oncological disorders and for solid tumours.

However, it has a range of adverse effects, including peripheral neuropathy, muscle adynamia, atony of the bladder, constipation and jaw pain. As a result vincristine is reserved for the treatment of life-threatening haemangiomas (20).

Laser therapy

One of the further modalities in the treatment of haemangiomas is laser therapy, which uses selective photothermolysis. The first use of lasers for this purpose began at the beginning of the 1980s. However, previously used types of lasers with continual regimes are linked with a higher risk of scarring. Several types of lasers have been tested, including the argon laser, Nd-YAG laser, CO2 laser, fractional photothermolysis and pulse colour laser (flashlamp-pumped pulse eye laser, PDL) (1, 6, 12, 16, 28). Of these lasers the most widely used is PDL, which emits light energy, which is absorbed by oxyhaemoglobin in the blood vessels. Treatment is performed generally in several sessions, 8 and more each 1-2 months (60).

In their study on 617 patients, Hohenleutner et al. determined that PDL halted progression in 97% of infantile haemangiomas, fully cured 14% and caused partial regression in a further 15% (41). It is highly effective in the treatment of ulcerated haemangiomas, in which it induces rapid re-epithelisation. However, in the case of proliferating haemangiomas it is limited by the depth of penetration. It

penetrates to a depth of approximately 1.2 mm. As a result this method is effective in the treatment of superficial haemangiomas. For this reason also naevus flammeus and a whole range of acquired cutaneous vascular lesions can be successfully treated with the help of PDL. In the case of IH it can be used on ulcerated haemangiomas, in which it reduces pain and induces re-epithelisation, in haemangiomas after involution it improves residual teleangiectasia.

Surgical treatment

Surgical intervention is an alternative for all the above -stated modalities (58). It is usually indicated in cases of residual cosmetic deformities in already regressed haemangiomas, or for lesions which are resistant to other less invasive methods of treatment. Primary excision, despite good bordering, is problematic in proliferating tumours due to the infiltrative nature of growth and the lack of a capsule.

Walker et al. (96) demonstrated effective clinical results following surgical removal in the case 12 visually significant haemangiomas, in half of which previous therapy had failed, but two of these also required postoperative transfusion due to haemorrhage. An important component of preoperative preparation is the imaging technique (MR, angiography), which clarifies the size, location and surgical risk for the surrounding orbitral structures, as well as typing of the patient's blood group.

Beta-blockers (general and topical application)

A shift in the treatment of haemangiomas occurred following the discovery of the efficacy of the non-selective beta-blocker propranolol in 2008 by the author Léauté Labreze et al. (62). This was thanks to a case of a patient treated for hypertrophic obstructive cardiomyopathy with peroral propranolol, after which a regression of the haemangioma was also recorded in the same child.

Beta-blockers act via three mechanisms: 1. vasoconstriction, 2. reduction of expression of VEGF and bFGF genes, 3. activation of apoptosis of endothelial cells. The last two mechanisms are probably responsible for the halting of proliferation and the acceleration of involution of the haemangiomas.

The effect was confirmed subsequently also in a further ten cases (seven of which had a periorbital localisation) following perorally administered propranolol (62). This systemic therapy demonstrated prospects for the therapy of large, deep or difficult to access lesions. Following on from this, dozens of case studies demonstrated positive results, including periocular cases. Taban and Goldberg (91) published successful treatment of a resistant orbital and periorbital haemangioma, whilst Fay et al. (23) successfully used propranolol as a primary therapy in the case of a deep intraconal haemangioma. Haider et al. (37) published a series of 17 patients with periocular haemangioma, in which they achieved halting of progression in 100% of cases, a more than 50% regression in 10 patients and a slight regression in 6 patients. Missoi et al. (67) demonstrated even more favourable results with reduction of size (median 61%) in all of 17 patients with periocular haemangioma treated with peroral propranolol. Although it is not specific for periorbicular lesions, one randomised, double-blind controlled trial exists comparing propranolol with a placebo. The trial determined that there was a halting of growth after 4 weeks in all patients using propranolol (versus 16 weeks in the case of the placebo) (40). Despite the effectiveness of this therapeutic modailty, there is a large risk of adverse side effects here. Propranolol may cause hypotension, bradycardia, bronchospasm, malfunction of glucose tolerance, congestive heart failure, hypothermia and sleep disorders. As a result it is necessary to monitor these children carefully (87). In the above-stated series of cases, treatment was discontinued in one patient due to systemic hypotension (13), and one patient suffered a benign episode of bradycardia. However, in the other cases propranolol was tolerated only with minor adverse effects such as gastrointestinal complaints, gastroesophageal reflux and fatigue (98). Additionally beta-blockers reduce lipolysis, glycogenolysis and gluconeogenesis. As a result careful monitoring during treatment and gradual discontinuation are necessary. Even if this method may appear to be the best available treatment, it is necessary to conduct further studies, and patients and their families should be appropriately instructed. A range of studies are currently ongoing, and further conclusive data shall be available.

Topical treatment

In an endeavour to minimise the side effects of systemic treatment, local beta-blockers have also been examined. Guo (35) published the first successful cases of the topical application of 0.5% timolol in the treatment of haemangioma, which however caused pronounced astigmatism. After 7 weeks of treatment, astigmatism was now anisometropic, there was a fundamental improvement in the size, thickness and colour of the infantile haemangioma. Subsequently a further 7 cases were published, in which a response was achieved in all within 4-8 weeks, with a reduction of the size within the range of 55-95% (72). None of these cases was linked with side effects. A larger, multicentric retrospective study examined 73 patients with smaller and superficial haemangiomas anywhere on the body, which were treated either with 0.1% or 0.5% timolol maleate gel applied twice per day (44). In one patient insomnia developed as a side effect, requiring discontinuation of medication. Overall the initial data indicates that topical beta-blockers may be safe and effective for the treatment of superficial lesions with a longer period of duration, by which a better effect is attained.

Intralesional application

There is a single publication on the intralesional application of beta-blockers (5). In this prospective, non-randomised trial, ten patients received an intralesional injection of triamcinolone 40 mg/ml and a further 12 patients received an intralesional injection of propranolol 1 mg/ml (up to 1 ml). In this uncontrolled study there were similar results with approximately 40% achieving an “excellent” response, 40-45% a “good” response and 17-20% without response. No adverse effects were reported. However, further examination of the safety and efficacy of intralesional application of beta-blockers would be necessary.

Radiotherapy

In the case of infantile haemangiomas resistant to medicamentous therapy, a low dosage of radiotherapy with coverage of the bulb is used at certain workplaces. Microembolisation, which is induced by radiation, accelerates the regression of the tumorous mass. Involution usually occurs after 1-2 weeks. In order to avert radiation complications it is necessary to monitor the accumulation of the dose (4, 6).

Cryotherapy

Cryotherapy has often been used for the treatment of superficial or combined haemangiomas. At present its use is in decline due to the more intensive use of lasers.

RESEARCH

Introduction

Infantile haemangiomas are regular benign tumours in children. The highest incidence of occurrence is in the area of the head and face (100). Periorbital haemangiomas incorporating haemangiomas on the upper eyelid, lower eyelid, inner corner, outer corner and orbital septum may suppress the bulb and also have an influence on the development of sight due to the potential occurrence of amblyopia. As a result timely intervention is necessary in order to prevent these negative consequences (82, 100).

Glucocorticoid therapy has a history dating back more than thirty years in the treatment of haemangiomas (31, 32). Studies demonstrated that intralesional injection of glucocorticoids in the case of periorbital haemangiomas brings good results with lesser side effects (49, 69, 78, 82, 98). The first studies from 2008 indicated substantial advantages of systemically used propranolol in the treatment of more severe haemangiomas (27, 62, 65, 85). Several studies have demonstrated the effectiveness of propranolol also in the case of periorbital haemangiomas (93, 94). To date no randomised controlled trial exists comparing two types of treatment for periorbital haemangiomas.

Objective

Retrospective analysis of treatment of periorbital haemangiomas at the Department of Paediatric Ophthalmology. The cohort comprised a total of 54 patients, who were observed from January 2009 to December 2014.

Method

The observed parameters covered: localisation of lesion, type of used therapy, age at time of determination of diagnosis, sex. In co-operation with the dermatology department at the Paediatric Clinic at the University Hospital in Brno, the diagnostic-therapeutic schema was as follows: MRI of the brain and orbit, fo-

Table 1 Division of orbital haemangiomas according to localisation. Total n = 54 patients

	Number of patients (n)	Number of patients (%)
Upper eyelid and eyebrows	26	48%
Lower eyelid	14	26%
Periorbital region	7	13%
Inner corner	4	7%
Choroidal haemangioma	3	6%

Table 2 Initial and percentage representation of individual therapeutic schemas in treatment of periorbital haemangiomas in observed cohort of patients. Total n = 54 patients

Type of represented treatment	Number of patients (n)	Number of patients (%)
Peroral beta-blocker propranolol	14	26%
Prednisone + propranolol	1	2%
Prednisone + intralesional DepoMedrol	3	6%
DepoMedrol monotherapy	1	2%
Surgical extirpation	3	6%
Cauterisation	2	4%
Prednisone monotherapy	3	6%
Observation without treatment	27	48%

Table 3 Division of patients with periorbital haemangioma according to sex. Total n = 54 patients

Sex	Number of patients (n)	Number of patients (%)
boys	22	41%
girls	32	59%

llowed by ultrasound examination of the stomach, cardiological and haematological examination. The initial dose of propranolol was 0.5 mg/kg/day p. o. (in 3 doses). During the course of application blood pressure, pulse and glycaemia were monitored. The dose was progressively increased up to the final dose of 2 mg/kg/day, divided into three doses with the same monitoring.

Subsequently checks of blood pressure, glycaemia and overall condition were conducted once per week at the outpatient department of a paediatric general practitioner. The treatment was conducted on average for 3 months (range 3-8 months). In the case of regression of the finding, the medicament was progressively discontinued, in the case of insufficient effect therapy continued.

Results

In 26 patients the lesion was localised on the upper eyelid (fig. 5) or in the area of the eyebrows, in 14 patients on the lower eyelid (fig. 3 and 4), in 7 patients in the periorbital region, and in 4 patients in the area of the inner corner. Choroidal haemangioma occurred in 3 patients. Table 1 presents a synoptic division of periorbital haemangiomas according to localisation of the lesion. The average age at the time of commencement of treatment was 3 months (range 3-8 months). In 14 patients the peroral beta-blocker propranolol was applied. A combination of a corticoid (preddnisone p. o.) and propranolol was used on 1 patient. A combination of prednisone and intralesional application of DepMedrol was used on 3 patients. For 1 patient we indicated monotherapy with intralesional Depo Medrol. Surgical extirpation was performed on 3 patients, and cauterisation in 2 cases. Monotherapy with prednisone was used on 3 patients. 27 patients were only observed without the need for therapy. Table 2 synoptically presents the initial and percentage representations of the individual therapeutic schemas in the entire cohort of patients. Table 3 presents a division of patients with periorbital haemangioma according to sex.

In the patients following intralesional application of corticoids (in monotherapy or in combination with another therapy), thus in a total of 4 patients, the tumours were reduced in size within one week of treatment. Within 4 months the tumour involuted. The tissue became soft and flatter. At present these tumours are in complete involution.

In 14 patients the tumour began to flatten within one to two weeks with systemic use of propranolol. One month later a marked reduction in size was observed. During treatment the tumour continually and gradually involuted. Treatment was conducted on average for 5.5 months. We did not record any repeat incidence of a tumour. Adverse

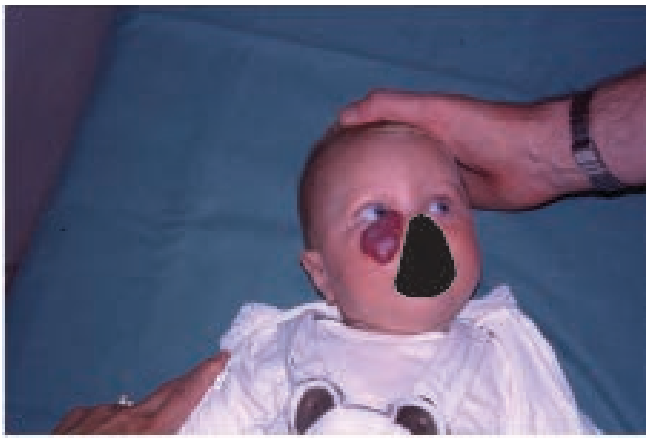

Fig. 3 Capillary haemangioma of the lower eyelid in a six month **old**

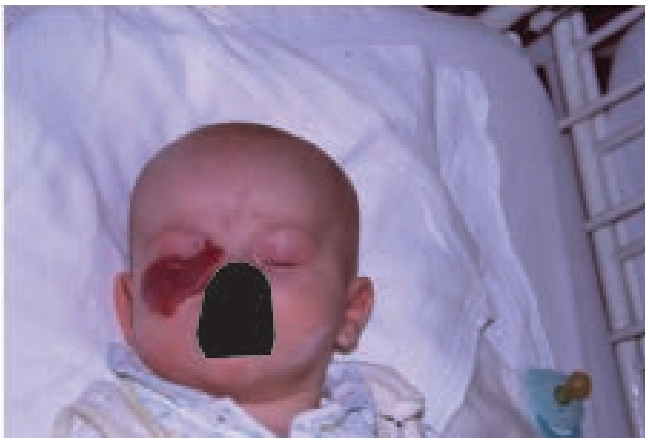

Fig. 4 Capillary haemangioma of the lower eyelid in a three month

Fig. 5 Superficial haemangioma of the right upper eyelid in a two month old infant before therapy

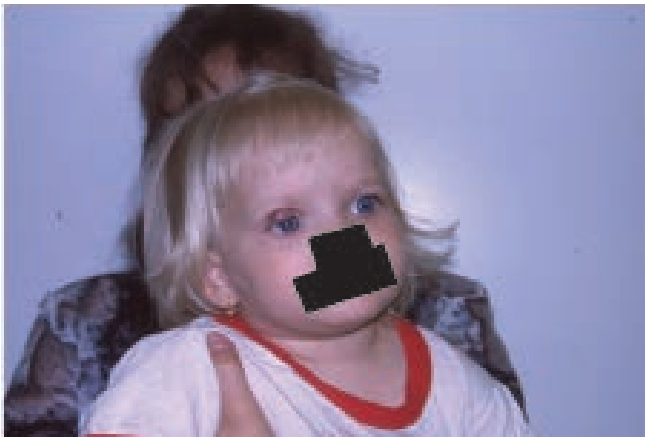

Fig. 6 Gradual regression of the finding following intralesional application of DepoMedrol

Fig. 7 Two year old girl after completion of treatment

effects in our cases were mild. In patients with intralesional application of glucocorticoids, one patient had mild atrophy of soft tissues, which returned to normal after 6 months.

Monotherapy with prednisone on three patients was terminated on average after 3 months. In one patient Cushing syndrome appeared as an adverse effect, the manifestations of which disappeared within 4 months following the termination of treatment. In one patient therapy with prednisone was accompanied with laser treatment and in another patient with peroral use of propranolol over a period of 4 months.

Surgical extirpation was performed on two patients without the need for further therapy. Due to the small size of the tumour, cauterisation was also sufficient for 3 patients.

No other systemic or local complications, such as retardation of growth, embolisation of the retinal artery, pigmentation or necrosis of the skin of the eyelids were recorded.

DISCUSSION

Periorbital haemangiomas rank among common benign tumours of the head and neck. However, they attract special attention due to the potential danger of worsening development of vision. Deformation of the cornea and indicated astigmatism caused by pressure of the tumour is the main cause of blunt sightedness (22, 69). In order to prevent its occurrence it is necessary to ensure rapid reduction of the tumour and release of the pressure on the cornea as soon as possible.

It was confirmed that good results were attained in the case of small haemangiomas by local injection of corticosteroids (78). Local injection of glucocorticoids into periorbital haemangiomas may support reduction of the size of the tumour and also accelerate the improvement of astigmatism. The majority of our patients were treated for a period of 4 months.

Systemically used propranolol was first used in the treatment of a more severe haemangioma in June 2008 (62, 85). A number of studies presented a satisfactory effect of systemic propranolol in the case of periorbital haemangiomas (93, 94). The authors also presented a further patient who was resistant to intralesional application of glucocorticoids and also responded to systemic propranolol (93). This indicates the superiority of propranolol in comparison with the effectiveness of intralesional corticoids (93, 94).

Overall the adverse effects on our patients are mild. In patients with corticoid therapy we recorded local atrophy of soft tissues in one patient, and Cushingoid manifestations in a patient to whom a systemic corticoid was applied.

CONCLUSION

According to our observations and the results of the previous studies it is possible to attain good results in the treatment of periorbital haemangiomas both by intralesional application of glucocorticoids and by systemic propranolol (48, 69, 82, 93, 94, 98). Systemic propranolol demonstrated superiority in terms of effectiveness and safety. Due to its adverse effects, propranolol is contraindicated for children with asthma, bronchitis or heart disease. In this case the choice remains intralesional application of glucocorticoids.

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