CASE REPORT

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Infantile hemangioma of the upper eyelid in one very and two extremely preterm infants

Infantilni hemangiom gornjeg kapka kod jednog veoma prevremeno i dva ekstremno prevremeno rođena odojčeta

Milica Žeravica*, Aleksandra Matić*†, Milan Matić*‡, Miloš Pajić*†, Sonja Prćić*†

***University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; †Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia; ‡University Clinical Center of Vojvodina, Clinic for Dermatovenereology, Novi Sad, Serbia**

Abstract

Introduction. Infantile hemangiomas (IHs) are the most common vascular tumors of infancy whose frequency increases with decreasing gestational age. Although rare, periorbital IHs (PIHs) have a high complication rate, with a substantial risk of impaired vision and aesthetic consequences. Because they are considered high-risk IH, such patients must be treated. In the available literature, there is little information about the treatment of IHs in very and extremely preterm newborns and infants. **Case report**. We present three male infants (one very and two extremely prematurely born) with PIHs involving the upper eyelid. In all three cases, IHs were solitary but with different subtypes according to soft-tissue depth (superficial, combined, deep). No additional congenital anomalies were found in any of these cases. An individualized approach to the management of each patient was applied. All infants were treated with oral administration of propranolol, with careful monitoring for potential side effects of the drug and adjustment of treatment, following their eventual occurrence. The introduction of oral propranolol was carried out in a hospital setting, with a gradual increase of the drug dose until the target dose was reached. **Conclusion.** In the case of PIH, an ophthalmologist is an inevitable part of the medical team. Very and extremely preterm infants are already under the supervision of an ophthalmologist due to mandatory screening for retinopathy of prematurity; however, if they also have PIHs, monitoring must be particularly detailed and long-lasting.

Key words:
drug therapy; eyelids; hemangioma; infant, extremely premature; infant, premature; propranolol.

Apstrakt

Uvod. Infantilni hemangiomi (IH) su najčešći vaskularni tumori u periodu odojčeta, čija se učestalost povećava sa smanjenjem gestacijskog doba. Mada retki, periorbitalni IH (PIH) imaju visoku učestalost komplikacija, sa značajnim rizikom od oštećenja vida i estetskih posledica. Zbog toga što se smatraju visokorizičnim IH, takvi bolesnici moraju biti lečeni. U dostupnoj literaturi ima malo podataka o terapiji IH kod novorođenčadi i odojčadi rođene sa veoma niskom i ekstremno niskom gestacijom. **Prikaz bolesnika**. Prikazujemo troje odojčadi muškog pola (jedno rođeno veoma prevremeno a dvoje ekstremno prevremeno) sa PIH koji je zahvatio gornji kapak. U sva tri slučaja, IH su bili pojedinačni, ali sa različitim podtipovima prema dubini zahvatanja mekog tkiva (površinski, kombinovani, duboki). Nijedan od prikazanih bolesnika nije imao dodatne kongenitalne anomalije. Za lečenje svakog bolesnika primenjen je individualni pristup. Sva odojčad su lečena oralnom primenom propranolola, uz pažljivo praćenje mogućih neželjenih efekata leka i prilagođavanje lečenja, u skladu sa njihovom eventualnom pojavom. Uvođenje propranolola *per os* sprovedeno je u bolničkim uslovima, sa postepenim povećavanjem doze leka do postizanja ciljne terapijske doze. **Zaključak.** U slučaju PIH, oftalmolog je neizostavni član medicinskog tima. Veoma nezrela i ekstremno nezrela novorođenčad su pod nadzorom oftalmologa u sklopu obaveznog skrininga na retinopatiju, ali, ukoliko imaju i PIH, nadzor mora biti posebno detaljan i dugotrajan.

Ključne reči:
lečenje lekovima; kapak; hemangiom; novorođenče, prevremeno, ekstremno; novorođenče, prevremeno; propranolol.

Correspondence to: Aleksandra Matić, Institute for Child and Youth Health Care of Vojvodina, HajdukVeljkova 3, 21 000 Novi Sad, Serbia. E-mail: aleksandra.matic@mf.uns.ac.rs

Introduction

Infantile hemangiomas (IHs) are the most common vascular tumors of infancy, which occur in as many as 5% of infants. They are benign vascular endothelial neoplasms that usually appear during the first weeks of life and go on to enter a proliferative phase, after which they show spontaneous regression – involution phase [1]. During the proliferative phase, which usually lasts from 6 to 12 months, numerous complications can emerge. The clinical significance of these complications is largely determined by the localization and type of IH, but some characteristics of the patient can also play an important role. We present three clinical cases of very preterm [born from 28 to 32 gestational weeks (GW)] and extremely preterm (born with less than 28 GW) infants with a solitary IH involving the upper eyelid. Through these case reports, we would like to point out the clinical characteristics and the approach to IHs of this particular localization and this specific group of infants.

Case report

All three presented infants were diagnosed, treated, and followed up in a single regional tertiary-care university hospital. Data on their prenatal history, birth, primary hospitalization, and the appearance, characteristics, therapy, and follow-up examinations of their IHs was retrospectively collected from their medical records, as well as from a photo archives database.

In all three cases, IHs were solitary without any accompanying anomalies, which was confirmed by repeated, detailed physical examinations, ultrasound of the brain and abdominal organs, as well as echocardiography. The diagnosis of IH, in all three cases, was established based on a typical clinical finding, aided by a Doppler ultrasound examination in the third patient shown.

The main perinatal data, IH characteristics, and therapy in all three clinical cases are shown in Table 1.

Case 1

In this case, we present a very preterm male infant, born at 30 GW with a birth weight of 1,570 g from a second spontaneously conceived pregnancy. He was born by an emergency cesarean section due to an acute illness of the mother. The infant suffered severe asphyxia at birth, requiring supplemental oxygen and noninvasive respiratory support. He was treated for several diseases associated with prematurity: respiratory distress syndrome (RDS), neonatal jaundice, late-onset sepsis, meningitis, and anemia of prematurity. Furthermore, regular screening for retinopathy of prematurity (ROP) revealed stage 1 ROP, with no need for intervention, and with the regression of changes on the retina at subsequent follow-ups.

At the postnatal age of 2 weeks, the infant developed an IH on his left upper eyelid. It was flat, with bright red papules on an erythematous background. There were also vasoconstriction patches and fine telangiectasias (Figure 1A).

During the next several weeks, the IH did not change in size. It was still at the level of the surrounding skin with an erythematous background, which was more pronounced while telangiectasias became coarser. Based on the evolution of the IH and its clinical appearance, it was classified as a superficial IH with minimal or arrested growth (MAG) – IH-MAG. At the age of 74 postnatal days, a nonselective beta-blocker – propranolol, was introduced in the hospital setting, accompanied by careful monitoring for potential adverse effects (AE) of the therapy. Propranolol was administered orally with a gradual increase of the dose to a therapeutic dose of 2 mg/kg divided into three equal daily doses. After reaching the target dose of propranolol, the infant was monitored on an outpatient basis, with the periodic dose adjustment of propranolol according to the infant's weight gain. Slow and subtle but progressive regression of IH was observed. At the postnatal age of six months, IH-MAG was paler and flat with no signs of ulceration (Figure 1B). On subsequent follow-up exams, further regression was observed with the continued propranolol therapy. No ophthalmological complications have been noticed so far.

Table 1

Infants' main perinatal data and clinical characteristics and therapy course of the upper eyelid infantile hemangiomas

Parameter	Case 1	Case 2	Case 3
Gestation (GW)	30	27 $^{5/7}$	27 $^{6/7}$
Birth weight (g)	1,570	1,010	1,150
Gender	male	male	male
Single-twin-triplet	single	triplet	twin
Mode of conception	spontaneous	IVF	IVF
Postnatal age (days, months/CGW) at the time of IH onset	15 days/32 GW	2.5 months/38 GW	21 day/30 $^{6/7}$ GW
Type of IH	superficial	combined	deep
Visual axis obstruction by the IH	no	yes	yes
Postnatal (days) and CGW/CA) of initiation of oral propranolol therapy	74 days/40 CGW	160 days/10 weeks CA	1st 66 days/ 37 $^{3/7}$ CGW 2nd 82 days/ 39 $^{4/7}$ CGW
Complications of oral propranolol therapy	none	none	apnea, hypoglycemia

GW – gestational weeks; IVF – *in vitro* fertilization; CGW – corrected gestational weeks; IH – infantile hemangioma; CA – corrected age.

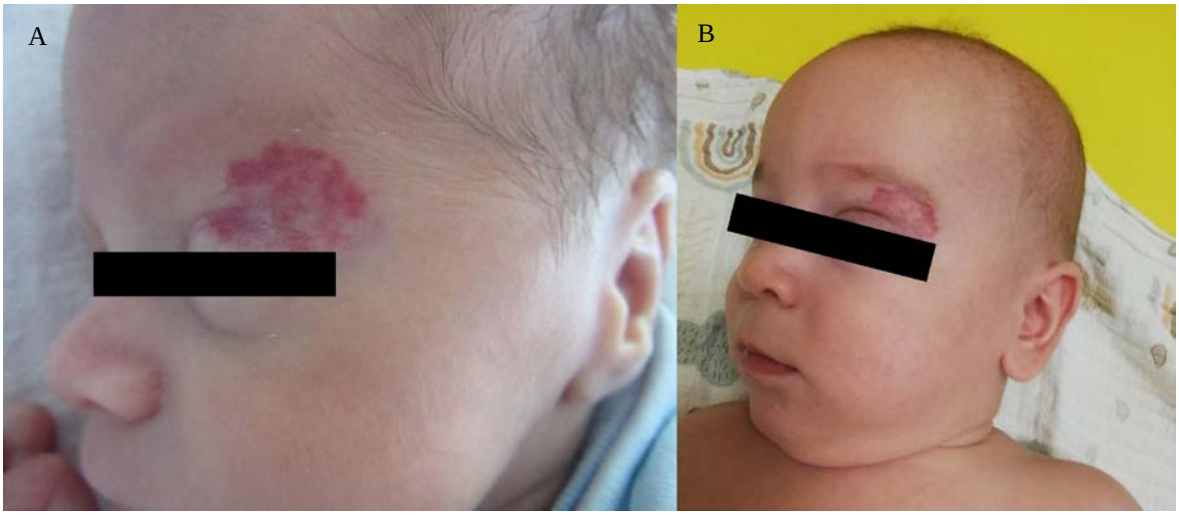

Fig. 1 – Patient 1 with the infantile hemangioma (IH) with minimal or arrested growth (MAG) – IH-MAG, on the left upper eyelid: A – at the postnatal age of 1 month, before propranolol therapy: IH appears as flat, with bright red papules on an erythematous background. Vasoconstriction patches and fine telangiectasias were also present; B – at the postnatal age of 6 months, after 3.5 months of propranolol therapy: IH-MAG was paler and flat with no signs of ulceration.

Case 2

In the second case, we present an extremely preterm male infant born at 27 $^{5/7}$ GW with a birth weight of 1,010 g as the second triplet from the first trigeminal pregnancy conceived through *in vitro* fertilization (IVF). He was born by an emergency cesarean section due to preterm contractions and the onset of spontaneous labor. The infant suffered severe asphyxia at birth, demanding resuscitation, endotracheal surfactant, and mechanical ventilation. He was treated for several prematurity-related complications: RDS, bronchopulmonary dysplasia (BPD), anemia of prematurity, late-onset sepsis, and intracranial hemorrhage grade I. Moreover, he suffered from a severe form of ROP treated with intravitreal application of vascular endothelial growth factor antagonist (anti-VEGF).

After he was discharged, at the postnatal age of about 2.5 months, his parents noticed a solitary red elevated lesion located on the right upper eyelid. At the postnatal age of 4.5 months, his IH was examined at our clinic for the first time during regular follow-up of the infant's neurodevelopment. At that point, an ill-defined, oval purple mass in the inner corner of the right upper eyelid was noted. The edge of the upper eyelid was deformed, and partial visual axis obstruction was evident (Figure 2). Since there were both superficial and deep components, the IH was classified as a combined IH.

Considering the interference with the visual axis, the infant was hospitalized in order to introduce oral propranolol therapy. The dose was gradually increased, reaching the target dose of 2 mg/kg, divided into three daily doses. Thereafter, the infant was monitored on an outpatient basis, with the periodic dose adjustment of propranolol. Very soon after the introduction of propranolol, a significant reduction of the IH was observed with complete regression after only 12 weeks of therapy. At the postnatal age of nine months, propranolol

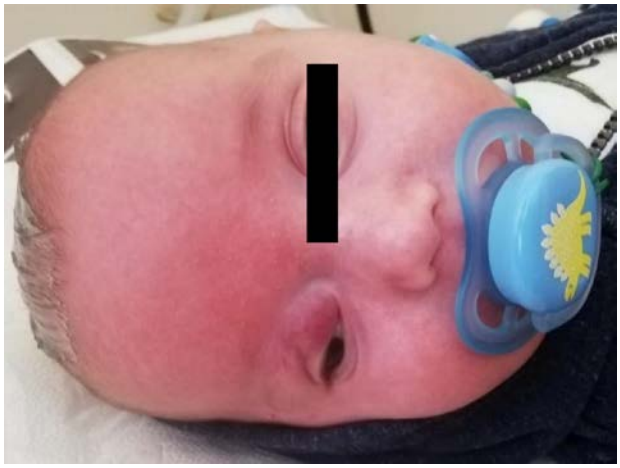

Fig. 2 – Patient 2 with combined infantile hemangioma of the inner corner of the right upper eyelid at the postnatal age of 4.5 months (before propranolol therapy): oval purple mass in the inner corner of the right upper eyelid was noted; the edge of the upper eyelid was deformed, and partial visual axis obstruction was evident.

was gradually discontinued. On subsequent follow-up exams, no IH rebound was noticed. Ophthalmological follow-up examinations did not show significant visual complications until the age of 15 months.

Case 3

In the third case, we present a male extremely preterm infant, the first-born twin conceived through IVF. He was born at 27 $^{6/7}$ GW by an emergency cesarean section due to eclampsia of the mother, with a birth weight of 1,150 g. At birth, the infant suffered severe asphyxia and RDS, demanding surfactant therapy and respiratory support. In the further course, besides late-onset sepsis and anemia of prematurity, he showed prolonged supplement oxygen dependency due to a severe form of BPD, treated with systemic corticosteroid therapy. In addition, he was diagnosed with severe ROP demanding treatment (intravitreal application of anti-VEGF).

At that time, an IH of the right upper eyelid was already present. It emerged at the postnatal age of 21 days in the form of large light blue–purple swelling covering the entire upper eyelid. Overlaying skin was intact, and fine telangiectasias were present. The IH was classified as a deep IH, and a decision on an active approach was made. Due to the previously mentioned complications of prematurity related to respiratory functions, systemic therapy of the IH with oral propranolol was postponed. In the meantime, the IH grew until it completely obstructed the visual axis, which was accompanied by excessive tearing (Figure 3). At the age of 66 postnatal days, during the primary hospitalization, the infant did not need supplemental oxygen and oral propranolol was introduced, starting with a dose of 0.5 mg/kg. However, on the second day of propranolol administration, apnea and hypoglycemia occurred, and propranolol therapy was discontinued. Following the stabilization of respiratory and metabolic functions, on the 82nd postnatal day (39 $^{4/7}$ corrected GW), another attempt was made to administer propranolol. The absence of previously noted AE enabled the gradual increase of the dose to the target therapeutic daily dose of 2 mg/kg divided into three equal daily doses. Soon after reaching the target dose of propranolol, the visual axis was partially opened. After discharge, the infant was carefully monitored on an outpatient basis, with the periodic dose adjustment of propranolol. Slow IH regression was noticed, almost completely freeing the visual axis. For precise monitoring of the regression of the deep portion of the IH, a magnetic resonance scan of the endocranium was performed after 12 months of propranolol therapy (at the postnatal age of 15 months). It revealed a significant reduction in volume of the IH of the right orbit and eyelid, with a minor retention in the cranial aspect of the orbital compartment. At the postnatal age of 17 months, IH of the right upper eyelid was still present, with consecutive discrete asymmetry of the *rima oculi*. Strabismus was noticed on ophthalmic follow-up visits. Visual evoked potential testing showed no significant deviation for age or asymmetry of the left and right eye.

Discussion

IHs are mostly found within the head and neck region, but the periocular area itself is rarely affected. In a population-based study, Alniemi et al. [2] calculated the occurrence rate of periocular IHs as 1 in 1,586 live births, with the IH being most prevalently located unilaterally on the upper eyelid. All three of our infants presented with an IH of the upper eyelid.

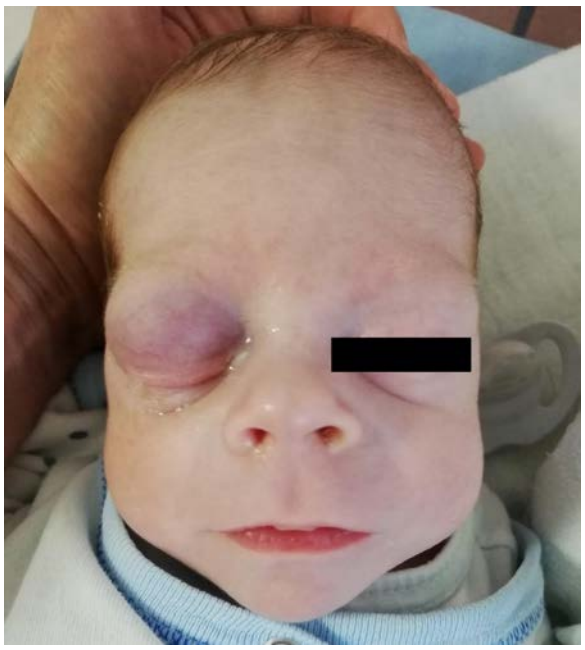

Fig. 3 – Patient 3 with deep infantile hemangioma (IH) of the right upper eyelid at the postnatal age of 2 months (before propranolol therapy): IH completely obstructed the visual axis, accompanied by excessive tearing.

The clinical significance of an IH is largely reflected by its localization as well as by its type regarding the anatomical spread and the depth of the affected tissue. Depending on the anatomic appearance, IHs may be categorized into four patterns: localized/focal (well-defined focal lesions), segmental (involving an anatomic region, often plaque-like and > 5 cm in diameter), indeterminate/undetermined (neither localized nor segmental), and multifocal (multiple discrete IHs at different body sites). IHs may also be classified with regard to soft-tissue depth as superficial (localized within the skin, with no evident subcutaneous component – appearing red in color), deep (located below the skin's surface, lower dermis or subcutis – appearing blue), combined/mixed (having both a superficial and deep component) [1]. A special subtype of superficial IH is referred to as IH-MAG, named after an important clinical characteristic – lack of an obvious proliferative phase [3, 4]. All of the presented infants had a localized or focal IH (ranging from 1–3 cm in maximal size) but with different subtypes according to soft-tissue depth, showing that all types of IH could be found on a small anatomic region.

Periorbital IHs (PIHs) have a high complication rate of 63%, which is nearly three times higher than that of the IHs located at other sites on the body [5].

Potential cutaneous sequels of high-risk IHs include anetodermic (outpouching) skin, redundant skin, and scarring (after ulceration) [6]. The incidence of ulceration of the IH surface varies from 5% to 21% and most commonly occurs in infants younger than four months, with preterm birth increasing the risk. IHs that are large, superficial or mixed, and/or segmental are more predisposed to ulceration [6]. The consequence of ulceration, besides pain, bleeding, or potential for a secondary infection, is the formation of a permanent scar. In addition to the aesthetic consequences of a scar on the eyelid, there is considerable risk for an incomplete closure of the eyelid due to the scar, and this, in turn, disrupts the function of the eye.

Furthermore, IHs on the eyelid pose a risk for vision impairment. Ocular complications such as ptosis, strabismus, anisometropia, astigmatism, and even amblyopia are not so rare in IHs involving the periocular region [1, 7]. During the infants' visually sensitive period, hemilateral visual deprivation leads to vision impairment, called "stimulus-deprivation amblyopia (SDA)" [8]. SDA can occur through direct pressure by the tissue mass of the hemangioma on the globe (causing astigmatism or myopia), by occlusion of the visual axis, or induction of strabismus due to mass effect [9]. Features of IHs of the upper eyelid associated with worsened visual outcomes are IHs greater than one centimeter, ptosis, proptosis, globe displacement, strabismus, and occlusion [9, 10]. Some IHs (mixed and deep IHs) may cause exophthalmos that can lead to exposure keratopathy and tear duct obstruction [9]. In preterm infants, especially those born with very and extremely small gestational age, vision function is already significantly impaired by prematurity. It is well known that premature infants, especially those with ROP, are at a significantly increased risk of a number of disorders of the eye and vision function, such as strabismus, myopia of prematurity, reduction of visual acuity, visual field deficits, deficits in contrast sensitivity, and vision loss [11]. An additional threat to such an important function for the quality of life as vision is the existence of a periocular IH, which is particularly burdensome in this subpopulation. Very and extremely preterm infants are already under the supervision of an ophthalmologist because of the need for ROP screening. However, if there is an additional risk factor for visual function, such as an IH of the eyelid, ophthalmologic monitoring must be particularly detailed and long-lasting since some visual complications can be confirmed only at a more advanced age.

Most low-risk, small, solitary IHs do not require any treatment. These low-risk IHs should be managed through an active non-intervention follow-up, with an emphasis on parental education on the nature of the IH [12].

According to the recently published Clinical Practice Guideline for the Management of Infantile Hemangiomas [1], those referred to as high-risk (HR) IHs require systemic treatment. If there is evidence or potential for IH to cause life-threatening complications, functional impairment or ulceration, structural anomalies, or permanent disfigurement, it should be classified and treated as an HR IH. Based on these criteria, the IH of the eyelid is certainly in an HR group and should be managed accordingly.

The first-line drug for HR IHs is orally administered propranolol [1], at a target dose of 2 to 3 mg/kg *per* day. With reports of up to 98% of IH responding favorably to treatment, propranolol is stated to be highly effective [6]. For all three cases, there was a clear indication for systemic therapy, bearing in mind the diameter greater than 1 cm, localization on the upper eyelid, and the burden of ocular complications.

Although propranolol is usually administered continuously for at least six months and maintained until 12 months of age [1], the duration of treatment is determined by a variety of factors, including age, hemangioma location, hemangioma subtype, and age at initiation of therapy [6]. Individualized approach is illustrated with the second presented infant, in whom propranolol therapy was withdrawn after only five months, with complete regression of IH and without IH rebound on long-term follow-up.

Propranolol has been proven to be very effective and safe for IH therapy [13, 14]. However, like any medicine, propranolol can cause side effects, among which clinically most important are hypoglycemia, hypotension, bradycardia, and bronchospasm [1]. These side effects are considered to be more frequent and more intense in such a specific and vulnerable group of patients as very and extremely preterm infants.

There is little information about the treatment of IHs (in general, as well as IHs of the periocular region) in very and extremely preterm infants. Most recommendations can be deduced from published papers and clinical experiences on term-born infants. The aforementioned guideline might be viewed as a stronghold for further investigation and trials in the pursuit of adequate treatment of this particular patient population, which is generally under a higher risk for the development of IHs, complicated IH course (ocular complications and ulceration), and increased risk of side-effects of the therapy. Very and extremely preterm infants are, in many aspects, especially demanding in the management of many

medical problems, IH of the eyelid included. The third infant in our case series showed AE of propranolol during the gradual increase of the dose, so it was temporarily discontinued to be administered at a later age. In this way, his eyelid IH grew, and his eye was occluded for a longer period than would be the case with the periocular IH of the same starting characteristics, appearing in a term infant at a later postnatal age.

Conclusion

IH on the eyelid must be considered high-risk and treated with systemic therapy as soon as possible. Significant risk of ulceration with consecutive scarring, eyelid deformity, and aesthetic consequences, as well as the possibility of a negative effect on vision function, requires treatment with the fastest and most complete effect; this effect can be achieved by oral beta-blocker therapy. The introduction of oral propranolol in preterm infants, especially those born very and extremely preterm, is best performed in a hospital setting, with gradual achievement of the target dose of the drug and careful monitoring of possible side effects of the therapy. An ophthalmologist is a mandatory part of the medical team for the follow-up of infants and children with infantile hemangioma on the eyelid, especially if they are preterm.

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