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Propranolol in the treatment of an extensive facial and orbital infantile hemangioma: case report

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Abstract
An infantile hemangioma, a common benign vascular tumor of infancy, can cause significant visual function impairment and/or relevant disfigurement. We report the successful outcome with oral propranolol treatment, with no adverse events related to the treatment, in a 2-month-old boy who presented with a complicated extensive infantile hemangioma of the right hemiface with deep intraorbital involvement, extending to the middle cranial fossa and pterygopalatine fossa.

Keywords: Infantile hemangioma, orbit, propranolol.

INTRODUCTION

Infantile hemangiomas are the most common benign vascular tumors of infancy. It has an incidence of 1 to 3% in newborns and 10 to 12% in children up to the first year of life. They are more common in Caucasian children, in females (female:male ratio of 3:1) and in premature infants (up to 30%). The diagnosis is based on clinical history and physical examination. Most hemangiomas have an uncomplicated benign and dynamic clinic course. Characteristically, they undergo a proliferative phase with significant growth and a rapidly increasing size of the lesion for several months, usually during the first year of life. After this period, there is a gradual involution phase, with a slow spontaneous regression over several years. It is estimated that the complete regression occurs at a rate of 10% per year, so that 30% would completely regress up to the age of 3 years, 50% up to the age of 5 years, 70% up to the age of 7 years and 90% up to the age of 9 years. On the other hand, an important minority of them may be associated with significant morbidity in early childhood. The most frequently involved regions of the body are the head and neck (up to 60%), followed by the trunk (25%) and the extremities (15%). Amblyopia, anisometropia, strabismus, proptosis, globe dystopia, exposure keratopathy and compressive neuropathy can be present in cases involving the eyelid and/or the orbit. Therefore, problematic facial lesions can cause severe visual impairment and/or relevant disfigurement, and require a therapeutic intervention (1).

Recently, propranolol has become increasingly popular as a successful treatment choice for complicated infantile hemangiomas, with few side effects comparing with other known therapies, namely systemic or intralesional corticosteroids, chemotherapeutic agents (vincristine, cyclophosphamide, alpha-interferon), radiotherapy, laser therapy, embolization, surgical intervention or a combination of treatments (2-4).

CASE REPORT

A 2-month-old boy was examined for an expansive hemangioma of the right hemiface, involving the subcutaneous tissue with superficial repercussion on the malar region and near the labial commissure. He had experienced progressive painless proptosis, superior and lateral displacement of the right ocular globe, along with fullness of the inferior eyelid for 1 month (figure 1).

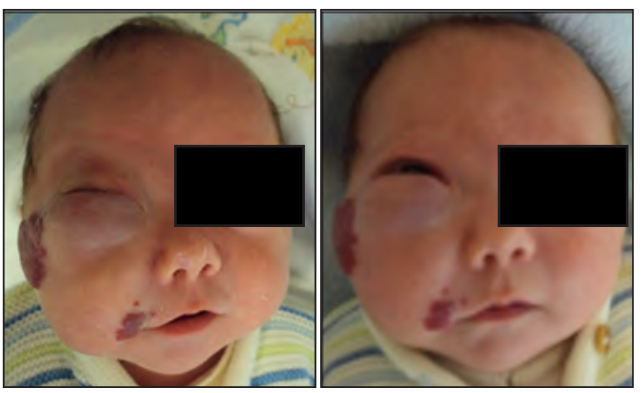

Figure 1. 2-months-old boy, before treatment.

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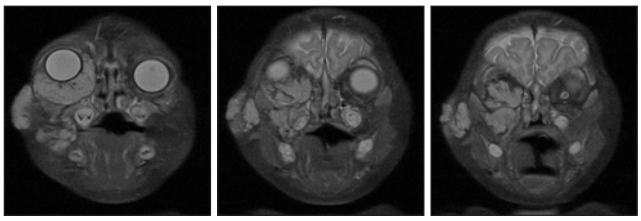

Figure 2. Coronal T2-weighted FSE craniofacial-orbital MRI images, before treatment.

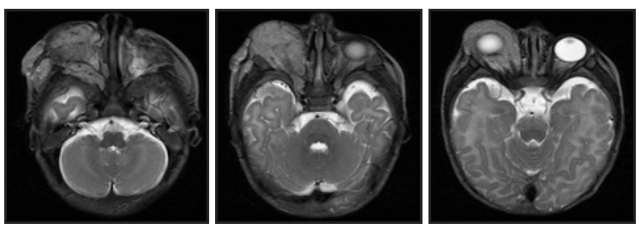

Figure 3. Axial T2-weighted FSE craniofacial-orbital MRI images, before treatment.

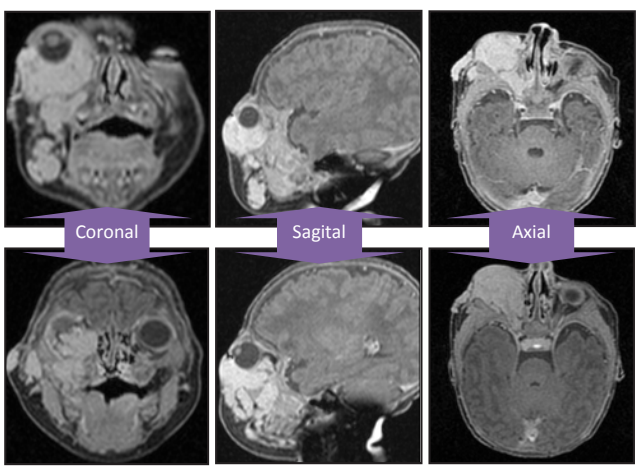

Figure 4. Gadolinium-enhanced T1-weighted SPGR craniofacial-orbital MRI, before treatment.

The assessment by magnetic resonance imaging (MRI) revealed a major deep intraorbital component, and a subcutaneous inferior periorbital component. It showed a voluminous intra and extraconal mass replacing the orbital fat, occupying almost the entire orbital cavity with higher expression on the medial and inferior aspect. The mass enwrapped the ocular globe posteriorly, the extraocular muscles and the optic nerve. It was found to spread to the middle cranial fossa through the superior orbital fissure; to the pterygopalatine fossa through the inferior orbital fissure; and to the eyelids anteriorly, with inferior predominance (figures 2-4).

A partial limitation of opening the right eye was noted. No relative afferent pupillary defect was detected. On ocular examination performed under general anesthesia, the anterior segment was normal, a mean corneal diameter of 10,5 mm was measured in both eyes; intraocular pressure were 20 mm Hg in the right eye and 18 mm Hg in the left eye, measured by the Perkins tonometer; and dilated fundus examination was normal in both eyes.

A detailed and extensive study was conducted, initially and during the frequent follow-up visits as required, including blood, urinary, imaging and others investigations, following a multidisciplinary approach, concerning evaluation and monitoring by several specialties (Departments of Pediatrics and Neonatology, Ophthalmology, Dermatology – Pedro Hispano Hospital, Porto; Departments of Pediatrics/Section of Haemato-Oncology, Pediatric Cardiology, Pediatric Surgery – São João Hospital, Porto).

Along with the craniofacial and orbital MRI assessment, others exams were managed. They were performed initially and repeated as required. A blood biochemistry and haematological profile, including a reticulocyte count and iron profile; a coagulation study; a urinary biochemistry and sediment; serologic and viral markers; a chest radiograph; abdominal, renal and pelvic ultrasounds; an electrocardiogram; an echocardiogram; an electroencephalogram; and visual evoked potentials; all were evaluated and no relevant findings were found.

No relevant systemic findings were found, aside from a right inguinal hernia corrected with a surgical intervention at the age of 6 months.

No record of relevant family or prenatal history.

At this time, with 2-months-old, he began treatment with systemic corticosteroids (prednisolone 2,5 mg/Kg/day).

At 5-months-old, the persistence of a major intraorbital component was found in a MRI reassessment, despite the relative improvement of the subcutaneous component. After the initial course of 3 months of systemic corticosteroids, this fact was considered an unsatisfactory clinical outcome, therefore oral propranolol treatment was started (2 mg/Kg/day, 3id) by gradual dose escalation. Systemic corticosteroids were gradually tapered, with complete suspension at 7 months of age.

Oral propranolol treatment was instituted initially on an inpatient setting, taking into account a rigid protocol established by the Departments of Pediatrics/Section of Haemato-Oncology and Pediatric Cardiology, at São João Hospital, Porto. Posteriorly, it was continued on an outpatient basis, also considering strict guidelines given to the parents. The outpatient follow-up visits were performed every 2-4 weeks by the pediatricians and every 4-8 weeks by the ophthalmologists, both of them initially more frequent.

At the 9-week follow-up visit after initiation of propranolol treatment and after the complete suspension of the corticosteroid therapy, the superficial component was significantly reduced in size and the proptosis less apparent.

At 24 months of age, 19 months after the initiation of propranolol treatment, a successful clinical and imaging outcome was registered. The hemangioma progressively regressed and disappeared, documented through MRI evaluation (figures 5-7). The ophthalmological examination was considered normal. The Hirschberg and Brückner tests were normal. A normal fixation behavior was noted through the *CSM* method (Central, Steady, Maintain).

The cover tests and the assessment of eye movements were normal. Another ocular examination performed under general anesthesia was carried out: the anterior segment was normal; intraocular pressure was 12 mm Hg in both eyes, measured by the Perkins tonometer; and dilated fundus examination was normal in both eyes.

Propranolol was discontinued through gradual tapering over a 2-month period.

During these 19 months of propranolol treatment, there was an attempt to lower the oral dosage, but the failure to show regression was noticed on an imaging reassessment at the thirteenth month of treatment, so the total oral dosage (2 mg/kg/day) was re-instituted.

There were no adverse events related to the treatment.

Currently, at the age of 3 years, he is on clinical surveillance every 4-6 months, and ten months after the discontinuation of propranolol treatment, no rebound growth was registered and the ophthalmological examination was considered normal.

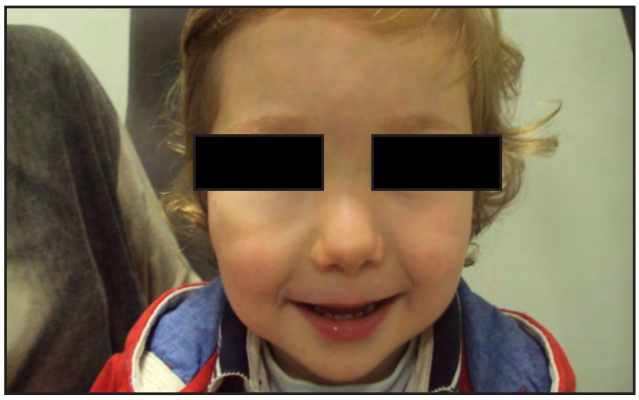

Figure 5. 24-months-old boy, after treatment.

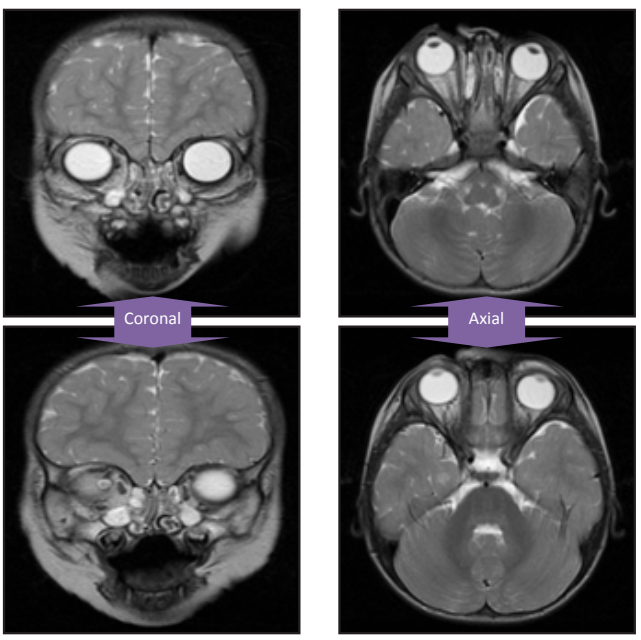

Figure 6. T2-weighted FSE craniofacial-orbital MRI images, after treatment.

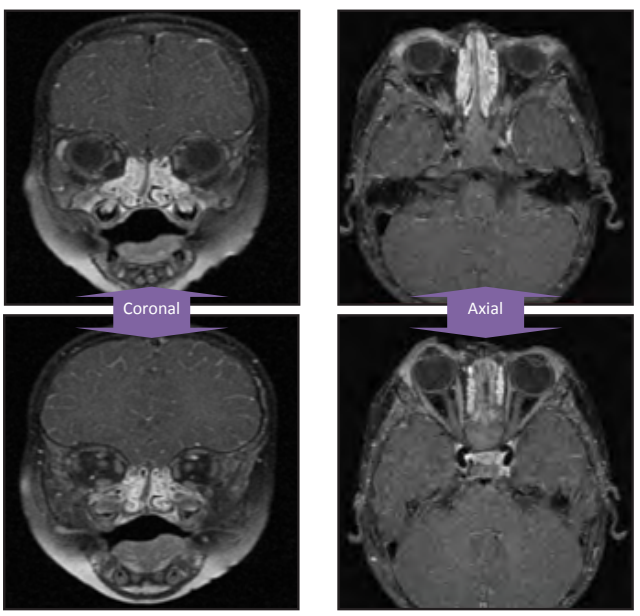

Figure 7. Gadolinium-enhanced T1-weighted craniofacial-orbital MRI images, after treatment.

DISCUSSION

Since 2008 when for the first time it was reported the efficacy of propranolol in inhibiting the growth and controlling the proliferative phase of problematic hemangiomas (2), some reports have been published that included hemangiomas with orbital involvement (6-9), but to the authors knowledge none was described as having the characteristics and extension of this portuguese case.

Such cases with deep orbital involvement may not be manageable with local therapies like intralesional corticosteroids injection, laser therapy or surgical intervention, given the potential risk of injury to the ocular globe, the extra-ocular muscles and the optic nerve. Systemic pharmacologic treatment with corticosteroids or chemotherapeutic agents may be associated with significant adverse events, with increased likelihood considering the duration of treatment.

The therapeutic effect of propranolol on hemangiomas, which are composed of a complex mixture of clonal endothelial cells (associated with interstitial cells as pericytes, dendritic cells and mast cells), is thought to be related with three different mechanisms: vascoconstriction, inhibition of angiogenesis and induction of apoptosis.

Epinephrine can cause both vasoconstriction and vasodilatation by activating both the α1 and β2 receptors, respectively. Propranolol has a β-blocker effect, without the α-antagonistic effect, and so inhibits the epinephrine mediated vasodilation, resulting in the vasoconstriction of endothelial cells. A clinical improvement is immediately visible as a change in color associated with a palpable softening of the hemangioma.

During the growth phase of hemangiomas, two major proangiogenic factors are involved and have their expression increased: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Still in this phase, histological studies have shown that both endothelial and interstitial cells are actively dividing. Some studies demonstrated that β-blockers can decrease the expression of bFGF and VEGF genes, which leads to the inhibition of angiogenesis, and thus might explain the progressive improvement of the hemangioma.

Apoptosis is a feature of the involution phase of hemangiomas. It is regulated by various pathways, with the probable involvement of the β1 adrenergic receptor. It has been hypothesized that the blockage of this β1 adrenoreceptor by propranolol, triggers apoptosis of capillary endothelial cells at an increased rate. This molecular mechanism might also explain the progressive improvement of the hemangioma.

Hypoglicemia, bradycardia, hypotension and bronchoespasm are well known potential side effects of propranolol, a non selective beta-blocker. They all can be adequately managed, fulfilling an initial pediatric assessment before initiation of therapy and monitoring such parameters throughout therapy with frequent pediatric follow-up visits (2-5).

In current literature, the duration of treatment with propranolol ranges widely, between 3 and 18 months, and supports discontinuation of therapy through gradual tapering at the end of the course over a 2-week period, to minimize the risk of a hyperadrenergic withdrawal response (5-10). In our patient, therapy was continued until complete resolution, treatment for 19 months, and propranolol was tapered through a 2-months period, given the registered fact of failure to obtain progressive regression at 13 months of treatment, during an attempt to lower the propranolol dose.

The successful outcome with no side effects in this patient, avoiding severe visual impairment during the critical period of visual development, supports the effectiveness of oral propranolol treatment for problematic hemangiomas, and possibly as a first line treatment in these cases.

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