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Review article

Propranolol treatment in life-threatening airway hemangiomas: A case series and review of literature

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ABSTRACT

Objectives: Infantile hemangiomas (IHs) in the airway may be potentially life-threatening during the proliferative phase. Available treatments like oral corticosteroids (OCS) and chemotherapeutic agents usually showed variable responses and serious side effects. Propranolol is a new and promising treatment option.

Methods: A case series of five IH patients with airway involvement is presented, supplemented with a review of literature. Propranolol treatment (2.0–3.0 mg/kg/day) was initiated between 3 weeks and 6 months of age. Three cases were treated with propranolol monotherapy, 2 cases with OCS primarily and propranolol secondarily, in which treatment with OCS could be reduced rapidly.

Results: In our case series a dramatic, fast response was observed in all cases, with a permanent effect after discontinuation in four cases. In one patient a relapse of airway problems occurred two months after discontinuation of propranolol at 16 months of age; this resolved after re-start of propranolol. Review of literature together with these five cases showed 81 patients with airway IHs treated with propranolol. Propranolol was effective in 90% of the cases and seven patients were classified as non-responders. Eight IHs relapsed while weaning of propranolol or after discontinuation; dose adjustment or restart was effective in most cases but one patient appeared resistant to therapy.

Conclusions: Propranolol seems to be a rapidly effective and safe treatment strategy for most IHs obstructing the airway. Because of the fast and important effects of propranolol, randomized controlled trials are hardly justifiable for this specific, relatively rare but, acute treatment indication. Despite the efficacy of propranolol, close monitoring of the patients with an airway IH is required, considering the risk of relapse of symptoms during or after treatment and the reported resistance to propranolol in at least 9% of the published cases. The dose and duration of treatment should be high and long enough to prevent relapse. Further research should focus on the optimal treatment protocol; the actual percentage of non-responders and also the mechanism of resistance to propranolol is unknown and needs to be illuminated.

Abbreviations: bFGF, basic fibroblast growth factor; CT, computed tomography; ECG, electrocardiography; ENT, ear nose and throat; GLUT1, glucose transporter protein 1; IHs, infantile hemangiomas/hemangiomas of infancy; LV, left ventricle; MRI, magnetic resonance imaging; OCS, oral corticosteroids; PHACES, acronym for posterior fossa brain malformations, hemangiomas of the face, arterial cerebrovascular abnormalities, eye abnormalities and sternal defects; RCTs, randomized controlled trials; RAS, renin–angiotensin system; SPECT, single photon emission computed tomography; VEGF, vascular endothelial growth factor.

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Contents

1. Introduction

Infantile hemangiomas (IHs) are true neoplastic proliferations of endothelial cells and the most common benign vascular tumors in children. An IH has the characteristic to proliferate rapidly in the first year of life. Most IHs proceed to resolution over a period of months to years without complications, not requiring any medical intervention [1]. The clinical significance of IHs varies widely and is often linked to their location, size and type. The predilection area for IH is the head and neck region; external compression of the airway or airway localization with obstruction may lead to life-threatening situations. Cutaneous signs of airway IHs typically are segmental skin lesions in a mandibular distribution ('beard hemangioma') in up to 50% of the patients. Patients usually present with stridor, respiratory distress or feeding difficulties [1,2]. Airway IHs can be evaluated by nasopharyngoscopy, laryngoscopy and/or magnetic resonance imaging (MRI). Multiple treatment modalities have been proposed in the management of airway IHs to maintain airway patency and to avoid tracheotomy and intensive care admission. Treatment options consisted of intralesional and systemic corticosteroids, chemotherapeutical agents (interferon or vincristine), laser therapy and/or open submucosal resection. Unfortunately, these treatment options have only limited therapeutic benefits with potential side effects and risks [3,4]. Until recently, systemic corticosteroid therapy was considered the first choice treatment in (airway) IHs but this therapy was not successful in many cases and entailed serious side effects like hypertension, growth retardation, Cushing face, and an increased susceptibility to infection [5].

The effect of the oral beta-blocker propranolol on IH is promising, described as a serendipitous finding by Léauté-Labrèze in 2008 [6]. Since then, several (case-) reports have demonstrated the effectiveness of propranolol in the treatment of IH, also in case of airway involvement. Potential modes of actions for propranolol in IH include vasoconstriction, a down-regulation of angiogenetic factors like vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) and an up-regulation of apoptosis of capillary endothelial cells [7]. More recently there is growing evidence that the renin–angiotensin system (RAS) plays an important role in the mechanism of action of propranolol for IH [8,9].

To provide definite evidence for the effect of propranolol on IH, randomized double-blinded controlled studies are most desirable. Nevertheless, case series are very useful to establish the role of new therapeutic agents. Several aspects regarding propranolol treatment for IH with airway involvement however remain to be illuminated: e.g. optimal dosage, duration and timing of therapy, effect on the natural course of IH, monitoring of short and long-term side effects and requirement of other treatment modalities.

We present five children with an airway-compromising IH treated with propranolol and a review of cases with airway IH treated with propranolol published in English literature. Finally, important issues and recommendations for the future will be discussed.

2. Clinical observations

2.1. Case 1

A two-weeks-old female neonate, born at term, presented a segmental IH, covering the right parieto-occipital skull, ear and neck. An ulceration (2 cm diameter), probably in the aplasia cutis spectrum was already visible at birth (Fig. 1a). Further examination revealed a grade II–III/VI high frequent systolic murmur, left parasternal, suspected for a ventricular septal defect (VSD). Oral antibiotics were given for 7 days and wound care was started. In the fourth week of life there was rapid expansion of the IH resulting in an inspiratory stridor and feeding difficulties. After ultrasonography showing a massive IH in the right neck region (right glandula parotis and parapharyngeal), the girl was referred to the intensive care unit of our tertiary center because of a threatened airway.

Propranolol was started in an increasing schedule to the target dosage of 3.0 mg/kg/day (in 3 doses). The inspiratory stridor disappeared within 24 h and discoloration of the skin localization of the IH was visible within a few days under stable hemodynamic controls and normal fasting glucose levels.

As part of the work-up for PHACES (posterior fossa brain malformations, hemangiomas of the face, arterial cerebrovascular abnormalities, eye abnormalities and sternal defects) echocardiography was performed; the left ventricle (LV) showed dimension on the 95th percentile and revealed a small VSD. During propranolol treatment however, the LV dimensions normalized. Electrocardiography (ECG), MRI of the head and ophthalmologic evaluation showed no abnormalities.

The IH improved dramatically in the following months (Fig. 1b). Propranolol was continued until 15 months of age and tapered in 3 weeks. Two months after discontinuation of propranolol, significant recurrence of swelling was observed with respiratory distress