Management of Infantile Hemangiomas of the Airway

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KEYWORDS
- Airway
- Subglottic
- Hemangioma
- Propranolol
- Surgery
- Management
- Laser

KEY POINTS
- Symptoms of airway hemangioma mimic those of croup, often resulting in a delay in diagnosis.
- Distribution of airway infantile hemangiomas may be focal or segmental. Segmental airway IHs are associated with cutaneous segmental IHs.
- Propranolol has largely supplanted steroids and surgical intervention in the management of airway hemangiomas.
- There is still a role for multimodality therapy for airway hemangiomas depending on the size of the lesion, location of the patient at the time of diagnosis, and response to medical therapy.

INTRODUCTION

Although infantile hemangiomas (IHs) are a common tumor of infancy, their occurrence in the airway is uncommon. When present, they may affect any portion of the airway; however, they most frequently involve the narrowest portion of the pediatric airway, namely the subglottis, often resulting in symptoms of stridor and respiratory distress. Unrecognized or untreated, the rapid growth of airway IHs may result in complete obstruction of the airway. As a result, otolaryngologists who treat children should be familiar with the diagnosis and management of these lesions (Fig. 1).

EPIDEMIOLOGY AND PATHOGENESIS

The incidence of airway IHs has not been determined in any formal study. An analysis of the 37-hospital Pediatric Health Information System database over the 5-year
period from 2001 to 2005 found that, of 2890 admissions for a primary or secondary diagnosis of IH, 337 (12%) underwent an airway procedure during at least 1 admission. Thus, on average, pediatric hospitals in this cohort likely treated fewer than 3 symptomatic airway IHs each year. In a 1967 series, IHs of the airway accounted for 1.5% of congenital laryngeal anomalies. As with IHs in general, airway IHs involving the subglottis have been reported more frequently in girls, with a 2:1 female-to-male preponderance. It is unknown if the other risk factors associated with IHs in general apply equally to the subset of IHs of the airway.

Fig. 1. Algorithm for evaluation and management of IH of airway. a In rare cases in which expert medical or surgical management is not readily accessible and symptoms are severe, placement of a temporary tracheotomy may be most expedient. OR, operating room.
The pathogenesis of IH of the airway remains incompletely established but is likely similar to that in IHs of other locations. A popular theory suggests that circulating endothelial progenitor cells find their way to certain locations that provide conditions favorable for growth into placenta-like tissues. The predilection for growth of IH in the airway and in the subglottis in particular has not been explained. Once endothelial progenitor cells are established in such tissues, they may encounter cellular signals and local tissue factors that stimulate their development. Such factors may include angiogenic and vasculogenic factors within the IH.8–10 It is also theorized that disturbances causing placental hypoxia trigger a vascular response that increases the likelihood of IH.11–13 In utero hypoxia is also the most common cause of low birth weight and may explain the association seen with premature delivery. Etiology and pathogenesis of IH are discussed in greater detail by Dr Denise M. Adams and Kiersten W. Ricci’s article, “Infantile Hemangiomas in the Head and Neck Region”, in this issue.

**CLINICAL PRESENTATION**

Airway IHs, similar to cutaneous IHs, may be described as focal or segmental (diffuse). Segmental airway lesions (Fig. 2) are typically associated with cutaneous segmental disease distributed along the mandible and chin (beard distribution). They may involve multiple mucosal subsites within the airway as well as paratracheal extension.14 Such lesions, as well as focal IHs involving the oral cavity and pharynx, may remain asymptomatic unless there is significant involvement of the larynx. Focal IHs of the larynx (Fig. 3), as

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**Fig. 2.** Segmental IH of airway. (A) Involvement of posterior pharyngeal wall, epiglottis, aryepiglottic fold, and arytenoid. (B) Involvement of left vestibular fold. True vocal folds are unaffected. (C) Right subglottic hemangioma. (D) Posterior membranous tracheal wall involvement. (From O TM, Alexander RE, Lando T, et al. Segmental hemangiomas of the upper airway. Laryngoscope 2009;119:2245; with permission.)
well as segmental lesions with laryngeal involvement, generally present with symptoms due to involvement of the subglottis; as a result, investigators have traditionally referred to these lesions as “subglottic hemangiomas”. Many of the latter have been shown to be transglottic lesions. 

Airway IHs are not generally symptomatic at birth but develop as the lesion proliferates during early infancy; 80% to 90% of affected babies present within the first 6 months of life, with a mean age of 3.6 months at diagnosis. As is the case with most masses of the subglottis, symptoms typically include biphasic stridor and barking cough in the absence of dysphonia. The symptoms may, therefore, be mistaken for those seen in more common disorders, such as infectious or inflammatory croup, especially because they typically worsen in the presence of upper respiratory illness. Furthermore, IHs respond to many of the same treatments used for croup, including racemic epinephrine and nebulized and systemic steroids. As a result, children may be symptomatic for several weeks before a definitive diagnosis is made. It is the recurrence or persistence of croup-like symptoms and progression of stridor during early infancy that suggest a diagnosis of airway IH and the need for additional investigation. Swallowing in children with airway IHs is usually normal; however, feeding may be affected as an infant tries to coordinate sucking with breathing.

Approximately one-half of infants diagnosed with an airway IH also have a cutaneous IH, although only 1% to 2% of children with cutaneous IHs also have airway IHs. The risk is substantially higher in individuals with PHACE (posterior fossa defects, hemangiomas, cerebrovascular arterial anomalies, cardiovascular anomalies including coarctation of the aorta, and eye anomalies) syndrome, among whom more than 50% have demonstrated airway involvement. Even in asymptomatic children, the presence of cutaneous IH in the beard distribution (parotid area, lips, chin, and neck [Fig. 4]) may be a predictor of IH in the airway, the highest risk associated with lesions in the median distribution (lower lip, lower gingiva, chin, and anterior neck). Such cases likely represent segmental IHs. IHs with a telangiectatic pattern seem to have the highest risk of airway involvement.

Once the proliferative phase is completed (6–12 months of age), respiratory symptoms tend to slowly resolve. Gradual spontaneous involution or regression of
cutaneous IHs starts by 1 year of age, and airway IHs generally follow this timeline as well. Although the duration of the involution process is variable, growth of a child over time allows the airway to better accommodate the IH, resulting in diminished frequency and severity of symptoms.

DIAGNOSIS

Because many congenital and inflammatory processes of the airway can mimic IH during the early months of infancy, diagnosis of airway IH begins with a high index of suspicion. The persistence or recurrence of croup-like symptoms and the presence of cutaneous lesions, especially involving the lower face, are important clues. When airway IH is suspected, diagnosis may be confirmed by either performing an imaging study or proceeding directly to laryngoscopy and bronchoscopy. Advocates of imaging prefer to make a presumptive diagnosis based on flexible airway endoscopy and confirm the diagnosis and assess the extent of the lesion by CT scan with angiography. This approach avoids the need for general anesthesia, especially because most airway IHs are now treated medically rather than surgically, but has the disadvantage of exposure to ionizing radiation at an early age. In most cases, the uncertainty of the diagnosis or the severity of symptoms necessitates a trip to an operating room, where the pathology may be visualized directly and treated surgically if necessary. This approach avoids the risks associated with radiation exposure. Office flexible endoscopy alone has also been successful in evaluating the airway below the vocal folds for IH in a cohort of high-risk patients.

When endoscopy is performed, symptomatic airway IHs are usually found to involve the subglottis, but bulk and blush may be present at adjacent and distant sites as well. Bulky lesions are smooth, submucosal, compressible, and pink or blue in color, often with surface telangiectasias (see Fig. 3). A left-sided predominance has been reported, but airway IHs may be bilateral, circumferential, or multiple. Biopsy is not usually necessary to establish the diagnosis; however, when the diagnosis is in doubt, specimens from true IHs stain positively for glucose transporter protein isoform 1 (GLUT1). The most useful and widely used immunohistochemical marker for the diagnosis of IH, GLUT1 is strongly expressed by IH endothelial cells and not by other benign vascular anomalies and has been validated for the identification of IHs of the airway.

On CT imaging, IHs demonstrate an intensely staining, well-circumscribed mass with lobular architecture. MR imaging, although often diagnostic, is less advantageous
because the duration of the study generally often requires general anesthesia. Fluoro-
scopy or anterior-posterior radiographs of the neck may demonstrate an asym-
metric subglottic narrowing; however; these studies do not definitively establish the
diagnosis.

A staging system for airway IHs has been proposed by Perkins and colleagues. A IH
stage is determined from CT angiography based on location, percentage of laryngeal
airway obstruction, and estimated total volume of the IH (Table 1). This staging system
is limited to lesions of the larynx and is not yet correlated with need for treatment or
prognosis.

MANAGEMENT

Once the diagnosis of airway IH has been established, the clinician must determine
whether intervention is required urgently and what type of intervention is most appro-
priate. Because involution is the ultimate fate of nearly all infantile IHs, watchful waiting
is reasonable for patients who are minimally symptomatic. For those patients with
more significant symptoms whose caretakers prefer no intervention for the lesion it-
self, tracheotomy with observation is highly successful. This approach, however, re-
quires a high level of maintenance to avoid tube occlusion, accidental decannulation,
exposure of the airway to water, and delayed communication skills.

As a result, in most cases, some sort of intervention for the IH itself is generally more
desirable. Lesions causing severe airway obstruction may require urgent surgical
reduction or intubation while awaiting pharmacologic therapy to take effect. In less se-
vere cases diagnosed by endoscopy in the operating room, intralesional steroids might
be considered to augment planned pharmacotherapy. Thus, the degree of airway
obstruction and the location of the patient at the time of diagnosis as well as the extent
of extralaryngeal IH, the experience of the treating physician, and the preferences of the
caretaker, are all considerations in determining the best course of action.

Pharmacotherapy

Over the past several years, propranolol has become the mainstay of pharmacologic
therapy for all IHs. In 2008, Léauté-Labrèze and colleagues first reported their seren-
dipitous observation that involution of IHs may be accelerated with the administration
of propranolol. At doses of 2 mg/kg/d to 3 mg/kg/d used to treat cardiac complica-
tions of their IHs, 2 children experienced marked and rapid involution of their IHs.
The following year, these same investigators reported additional treatment successes
using propranolol in 32 patients with IH. The efficacy of propranolol in treating cuta-
aneous IH is now well established in systematic reviews and meta-analyses of clinical

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<th>Table 1</th>
<th>Proposed airway infantile hemangioma staging system and treatment protocol</th>
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<td>Stage</td>
<td>Unilateral Airway Hemangioma</td>
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<td>2</td>
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* Stage based on lowest stage in a row with two or more positive findings.

From Perkins JA, Chen EY, Hoffer FA, et al. Proposal for staging airway hemangiomas. Otolar-
nygol Head Neck Surg 2009;141:519; with permission.
reports,37,38 large cohort studies,39 and randomized clinical trials.40,41 Propranolol has also been used successfully in the management of airway IHs.42–56 Response is not universal, however, and symptoms may recur while on the medication or during weaning, with reported symptom recurrence rates as high as 50%.52–54,57,58 An oral formulation free of alcohol, sugar, and paraben (Hemangeol; Pierre Fabre; Castres, France) has been approved by the US Food and Drug Administration for use in children.41

Proposed mechanisms by which propranolol inhibits IH growth include inhibition of vasculogenesis, blocking of proangiogenic signals (vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinases 2 and 9), inactivation of the renin-angiotensin system, vasoconstriction due to decreased release of nitric oxide, and induction of apoptosis in proliferating endothelial cells.36,59–61 It has also been suggested that propranolol may prevent the differentiation of IH stem cells into endothelial cells or pericytes62 or that it may hasten the differentiation of progenitor cells into adipocytes.42

The pretreatment assessment, optimal dose, and appropriate duration of propranolol therapy vary considerably in the literature. Contraindications to use of the drug include cardiogenic shock, sinus bradycardia, hypotension, heart block greater than first degree, heart failure, bronchial asthma, and known hypersensitivity to the drug. Once these disorders are ruled out, most clinicians perform a cardiac evaluation, assess baseline heart rate and blood pressure, and determine whether additional input from a cardiologist is indicated. Pretreatment cardiac screening seems of limited value in patients with an unremarkable cardiac history and examination.63,64 Pretreatment electrocardiography is recommended, however, for patients considered at high risk for potential cardiac complications.60 Special precautions have been suggested for children diagnosed with PHACE syndrome and significant intracranial vascular anomalies because of the theoretically increased risk of acute ischemic stroke.60 In most series, the drug is started at a dose of 1 mg/kg/d to 2 mg/kg/d divided 2 to 3 times a day and then increased over several days to a week to 2 mg/kg/d to 3 mg/kg/d. Heart rate and blood pressure are checked each hour for the first 2 hours after the initial dose and with each dosage increase. The drug is usually administered throughout most of the first year of life. Although a consensus multidisciplinary protocol has been published,60 protocols for propranolol initiation authored by otolaryngologists have also been published in the otolaryngology literature.65,66 There is a single report of successful use of intravenous propranolol for airway obstruction in a critically ill neonate with a large cervicofacial IH.67 It has been suggested that propranolol should become the standard for initial management of all airway IHs.58

Propranolol has a well-established safety profile based on years of use for control of high blood pressure and cardiac pathology. Additional safety information specifically regarding the use of propranolol in IH comes from the adverse effect data from the Hemangeol trial41 as well as a recent systematic review.69 The most common propranolol-related adverse effects are diarrhea (approximately 19%), peripheral coldness (approximately 7%–8%), and a variety of sleep disorders (approximately 2%–6% each).61 Other potentially significant adverse effects include bronchospasm, bronchiolitis, and asymptomatic hypotension. Rare but potentially serious side effects include bradycardia, exposure of an undiagnosed atrioventricular block, and hypoglycemia.41,69 Temporary discontinuation of oral propranolol therapy is recommended in cases of poor oral feeding, diarrhea, and obstructive bronchitis. Rebound growth after discontinuation of therapy has been observed in 6% to 25% of children, often well after their first birthday, leading some clinicians to wean propranolol over weeks to months.70–74
Although propranolol has largely supplanted systemic corticosteroids as first-line pharmacotherapy, the latter are occasionally useful in refractory cases. Steroid medications inhibit growth of the lesion during the proliferative phase, by inhibiting vasculogenesis and promoting adipogenesis. These drugs lose their effectiveness once involution begins. Doses of prednisolone at 2 mg/kg/d to 3 mg/kg/d are generally necessary to control growth of the mass and should be maintained for one to 2 weeks before starting a 2-week to 4-week taper. Response rates reported in the literature vary between 30% and 93%, although there is little consistency among dosing regimens. Long-term management on steroids carries a significant risk of complications, including gastroesophageal reflux, gastritis, immune suppression, cushingoid changes, hyperglycemia and glycosuria, hypertension, fluid and electrolyte disturbances, and growth retardation. IH patients on maintenance steroids should concomitantly receive courses of H2-receptor blockers and trimethoprim-sulfamethoxazole as prophylaxis against gastritis and pneumocystis carinii infection, respectively. Live vaccinations should also be avoided while a child is taking high-dose steroids.

Interferon α-2A is mentioned for historical reasons because it has been used with success in treating IHs, but this drug should only be considered when all other traditional modalities fail. Potential side effects associated with this therapy include fever, myalgia, transient elevation of hepatic transaminase levels, transient neutropenia, anemia, and spastic diplegia.

Surgical Intervention

Indications for surgical management of airway IH have become few since the efficacy of propranolol was established. Surgery is a reasonable consideration when (1) the obstruction found at operative endoscopy is severe and likely requires a lengthy intubation while medical therapy is initiated and (2) the patient remains severely symptomatic despite an adequate trial of medical therapy.

Operative intervention may include intralesional injection of corticosteroids and/or partial ablation of the IH or complete surgical excision of the portion of the lesion within the airway. In most cases, the patients remain on medical therapy postoperatively to reduce the likelihood of recurrence. This is of particular importance in segmental airway lesions with known extension outside of the airway.

Intralesional steroids should be considered for patients whose IHs have necessitated a trip to the operating room for endoscopy or endoscopic resection. Although repeated injections are usually necessary as single-modality therapy, these medications may be effective adjuvant therapy for patients whose lesions are being observed, treated pharmacologically, or partially resected. In most cases, triamcinolone, 40 mg/mL, is administered at a dose of 3 mg/kg to 5 mg/kg either alone or supplemented by betamethasone, 6 mg/mL, dosed at 0.5 mg/kg to 1.0 mg/kg. Total volume delivered may be limited by the size of the lesion, and care must be taken to avoid depositing the steroid medication deep enough to affect the underlying cartilage. Patients usually require at least overnight intubation due to the increased volume of the lesion after injection. Cure rates of 77% to 87% using intralesional steroids have been reported.

Airway IHs causing focal obstruction may be addressed surgically by a subtotal endoscopic approach using a microscope or telescope or by total excision through an open approach, dividing the thyroid and cricoid cartilages in the midline. Subtotal resection, more often than total excision, carries the risk of growth of the residual lesion during the proliferative phase, potentially resulting in additional surgical procedures unless combined with pharmacologic therapy. Endoscopic excision is usually performed using an apneic anesthesia technique, intermittently interrupting the surgery for reinsertion of the tube and ventilation of the patient. Alternatively, the
procedure may be performed under spontaneous ventilation with anesthetic insufflation or Venturi jet ventilation.

The laser has been the most popular endoscopic surgical modality,\textsuperscript{15} with the carbon dioxide (CO\textsubscript{2}),\textsuperscript{4,6,17,84–86} potassium titanyl phosphate (KTP),\textsuperscript{87,88} and Nd:YAG lasers all demonstrating some effectiveness. All these lasers are currently available for airway use through fiber delivery systems; however, only CO\textsubscript{2} is used by direct beam. CO\textsubscript{2} lasers are preferentially absorbed by water, whereas KTP and Nd:YAG lasers take advantage of absorption peaks that approximate those of hemoglobin and are thought to penetrate more deeply. All of these lasers, however, cause destruction by ablation rather than selective photothermolysis. As a result, in addition to the risk of recurrence, laser treatment carries a risk of subglottic stenosis of 5% to 25% that is likely greatest with deeper resections and in cases of bilateral or circumferential disease.\textsuperscript{6,23,91} Debulking of the lesion using rotary powered instrumentation (microdébrider, or shaver) has also been reported.\textsuperscript{92,93} Postoperatively, patients are observed in an intensive care setting. Some clinicians recommend face tent humidification to prevent airway obstruction due to eschar formation.

Although the first open surgical excision of a focally obstructing airway IH was reported in 1949, the procedure did not gain popularity until the 1990s, after complications of laser therapy became increasingly apparent.\textsuperscript{94–99} Over the 15 years prior to the discovery of effects of propranolol, open resection seemed to be emerging as the intervention of choice for airway IHs. The procedure is of greatest advantage in patients with bilateral or circumferential lesions that may otherwise have been at risk for postoperative stenosis, recurrence, or tracheotomy. Some investigators have found the procedure useful for their propranolol failures, which may be as high as 50%.\textsuperscript{58} Open surgical excision may be more difficult, however, in cases involving significant extralaryngeal extension, and the procedure may potentially result in some degree of dysphonia.

After initial intubation through the obstructed portion of the airway, the lesion is approached through the anterior neck via laryngofissure. After the tube has been relocated to the inferior aspect of the incision, the IH is removed submucosally under the operating microscope. At the conclusion of the dissection, the patient is intubated; in some cases, a thyroid cartilage graft may be placed to enlarge the subglottic laryngeal framework. After the neck is closed, the patient is transported to the ICU where intubation is maintained for 3 days to 7 days.

REFERENCES