The treatment of hemangioma of the larynx in children is still a dilemma

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INTRODUCTION

The hemangioma of the larynx in children is rare benign vascular neoplasm, which by its localization may have malign clinical course. Last year the American Academy of Pediatrics (AAP) made recommendations for the treatment of infantile hemangioma while calling for additional research of the treatment of hemangioma in the airways of young children [1].

CASE REPORT

We rarely encounter a larynx hemangioma, especially if there is no accompanying hemangioma of the skin [2]. However, we report a case of a male child aged 15 months with the diagnosis of larynx hemangioma. We were even more confused by the normal findings of fiber-laryngoscopy. However, the pediatricians had to treat the child until fiber-bronchoscopy was performed. The question is which drug to use? Which drug may contribute to a successful differential diagnosis of the mentioned condition in a primary health care, before fiber-bronchoscopy is done? Are the AAP recommendations absolutely relevant [1]?

A brief description of the clinical course of hemangioma of the larynx in a boy will be the basis for monitoring the treatment course and making conclusions. Before admission to the Pediatric Clinic, the 15-month-old boy had a cough, breathing difficulty and a fever of 38.6°C, which was treated by nebulized bronchodilator with fenoterol and ipratropium Bromide (FIB) and a steroid therapy (Table 1). On admission, the boy had signs of respiratory insufficiency. The majority of biochemistry, hematological and microbiological analyses (Table 2) were within border references for his age [3]. At back-front chest X-ray in the projection of the larynx a hyperdense zone could be seen (Figure 1), asymmetrical, with successive extensions first to the left, then to the right, followed with air bronchogram and the strip-blotchy shadows in the lung parenchyma on both sides. The X-ray of the trachea in two directions and a contrast X-ray of the esophagus did not present any abnormal findings.

After three days of therapy (Table 1), a pediatrician considered that the child’s condition was improving and did not need further epinephrine inhalation. However, about eight hours after epinephrine was excluded, his condition deteriorated. Since the finding of fiberoptic laryngoscopy to the borders of the larynx were a normal, fiberoptic bronchoscopy was performed (Table 1) as multidetector computed tomography (MDCT) (Figure 2). MDCT at the level of cervical vertebral body 2–3, on the left airway wall, discovered a thickening and hypodense, polypoid change, which asymmetrically narrowed the lumen of the border between the larynx and the trachea to a minimum diameter of under 2 mm. After that, Propranolol was introduced to the therapy, and after four days, oxygen therapy was no longer needed. After ten days of propranolol treatment, fiberoptic bronchoscopy was
Table 1. The clinical course and treatment of hemangioma of the larynx in a boy with body weight of 9.5 kg

| Day of treatment | Level of health care | Primary care | Pediatric Clinic | Institute for Mother and Child Healthcare |
|------------------|----------------------|--------------|------------------|-------------------------------------------|
| 1                | Day 1: cough, breathing difficulty, fever 38.6°C | Day 5: cough, dyspnea, inspiratory stridor, pallor of skin and visible mucus membranes, fluttering nostrils, SaO₂ 89–96% (according to the phase of the respiratory cycle and waking/sleeping child), RR 36/min, and HR 150/min. Apart from hyperglycemia (8.1 mmol/l), other biochemical, hematological and microbiological analyses were within border references for the child's age [3]. | Day 12: Respiratory failure and inspiratory stridor continued to worsen; Fiberoptic bronchoscopy revealed a cystic tumor covered with normal mucus membrane color, capillary with a strong drawing, located under false vocal cords on both sides predominantly to the right, where it occupied the entire space between the anterior and posterior commissure, and left behind the last commissure with a tumor on the right almost completely obstructing aditus of larynx, leaving a breathing crack in the back commissure, which corresponds to the findings of hemangioma of the larynx. MDCT scanners neck and chest and with i.v. application of contrast medium: precisely determined the level of localization of lesions in C2–3 vertebral body, on the left wall, in the form of thickening and polypoid hypodense change which narrowed asymmetrical the lumen of the larynx to the smallest diameter of about 2 mm. | |
| 2                | Day 2–3: cough, breathing difficulty | | | |
| 3                | Day 4: more powerful cough, hoarse, fever 38.8°C | Day 6: cough, dyspnoea, inspiratory stridor, pallor of skin and visible mucus membranes, fluttering nostrils, SaO₂ 89–96% (according to the phase of the respiratory cycle and waking/sleeping child), RR 36/min, and HR 150/min. Apart from hyperglycemia (8.1 mmol/l), other biochemical, hematological and microbiological analyses were within border references for the child's age [3]. | | |
| 4                | | Day 7: biphasic stridor, SaO₂ < 89%, RR 28/min, HR 90/min. X-ray of the trachea in two directions and contrast x-ray of the esophagus did not present abnormal findings. | | |
| 5                | Some clinical features and additional diagnostic findings per days | | | |
| 6                | | | | |
| 7                | | | | |
| 8                | | | | |
| 9                | | | | |
| 10               | | | | |
| 11               | | | | |
| 12               | | | | |
| 13               | | | | |
| 14               | | | | |
| 15               | | | | |
| 16               | | | | |
| 17               | | | | |

### Drugs:

| Drug                        | Primary care | Pediatric Clinic | Institute for Mother and Child Healthcare |
|-----------------------------|--------------|------------------|-------------------------------------------|
| FIB, sol. (ml), nebulized   | 0.2/12h      | 0.2/6h           | 0.2/6h                                    |
| Salbutamol, sir.(ml), p.o   | 2.5/8h       | 2.5/8h           | 2.5/8h                                    |
| Epinephrine 1:10000 (+ panthenol + saline) (mg/kg/dosis) nebulized | 0.1/4h       | 0.1/4h           | 0.1/4h                                    |
| Aminophylline, i.v. (mg/kg/4h) | | | |
| Salbutamol, sir. (mg) nebulized | | | |
| Ipratropium bromide, sir. for inhalation (μ/kg) | | 0.2/4h | |
| Magnesium sulfate, i.v. (mg/kg) | | 5/4h | |
| Budesonide (μ/12h), nebulized | 250 | 250 | 250 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Dexamethasone i.v. (mg/dosis/d divided in two doses) | 8 | 8 | |
| Methylprednisolone i.v. (mg/kg/d divided in three doses) | | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| Antibiotics                 | | | |
| Azithromycin, p.o            | | | |
| Clarithromycin, p.o          | | | |
| Propranolol (mg/kg/d) divided in 2 doses, p.o. | | 2 | 2 | 2 | 2 | 2 | con | 2 | 2 | 2 | con | |

FIB – fenoterol and ipratropium bromide; p.o. – orally; SaO₂ – percutaneous oxygen saturation; RR – respiratory rate; HR – heart rate; MDCT – multiple detector computed tomography; C – cervical; i.v. – intravenous; con – continued; – interrupted

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repeated revealing a significant reduction in tumor tissue and the reappearance of sufficient breathing space (Table 1). The child was discharged home with the same dose of Propranolol (for the total of six weeks), which resulted in recovery.

**DISCUSSION**

In a 15-month-old boy with hemangioma of the larynx, there was a good therapeutic response after administration of epinephrine and propranolol. There was no improvement of respiratory failure after the administration of corticosteroids (systemic not inhaled), which is recommended in many textbooks of pediatrics and is placed as the first therapeutic option for laryngeal hemangioma [2]. There was no desired therapeutic response after the administration of a bronchodilator (beta-2-agonists, theophylline), or a broad-spectrum antibiotics (Cephalosporins 3rd generation, Macrolides). Epinephrine treatment in inhalation for three days resulted in clinical improvement. Epinephrine therapy was discontinued because no therapeutic protocol in pediatrics recommends the use of a multi-day inhalation of this drug [2].

Epinephrine causes vasoconstriction of arterioles and the dilatation of airway smooth muscle that in a short period of a few hours can impose beneficial effects on blood vessels in the hemangioma, and the dilatation of the larynx. However, systemic and daily use of epinephrine for seven days causes ischemic effect on the soft tissues, which is a powerful stimulus for neovascularization [4, 5]. This effect is not desirable in the treatment of hemangioma of the larynx, which leads us to think that epinephrine should be administered for a very short period, i.e. until the clinical improvement of respiratory insufficiency becomes definite. At the same time, the speed of therapeutic response to epinephrine helped us in the differential diagnosis of inspiratory stridor and a hoarse cough. The duration of epinephrine administration is not defined in the recommendations of the AAP, so future research is needed [1].

The peripheral effects of propranolol are used to “shrink” a hemangioma and to prevent the differentiation of infantile hemangioma stem cells to endothelial cells and pericytes [1, 6]. The recommendation is that the initial dose of propranolol per os for the larynx hemangioma would be the same like for skin hemangioma: 1–3.4 mg/kg/d with a gradual reduction in dose during 3–12 months, until the child reaches the age (8–12 months of age) when a spontaneous resolution of infantile hemangioma occurs [1, 2]. However, we have applied a dose of propranolol 2 mg/kg/d, continuously to the patient for six weeks only and achieved a complete resolution of hemangioma of the larynx without any side effects like drowsiness or hypoglycemia.

Despite the official recommendations concerning the effective application of steroids in the treatment of infantile hemangioma of the larynx, our experience was not positive [1, 2] (Table 1). Only after adding propranolol for four days, the need for oxygen was eliminated and the child

Table 2. The 15-month-old boy’s laboratory findings on admission to the Pediatric Clinic [2]

| Test                        | Value             |
|-----------------------------|-------------------|
| Gas analysis by Astrup from venous blood: pH 7.34, pO2 5.7 kPa, pCO2 5.9 kPa, sodium ionized 138 mmol/l, potassium ionized 4.3 mmol/l, calcium ionized 1.14 mmol/l, bicarbonate 24 mmol/l, base excess -2 mmol/l |
| Sedimentation rate 10, C-reactive protein 9.9 mg/l |
| Complete blood count: WBC 5.1x10^9/l, neutrophils 0.53, lymphocyte 0.43, monocytes 0.05, PLT 267x10^9/l, RBC 4.64x10^12/l, Hb 117 g/l, Hct 36% |
| Urinalysis – normal |
| Glycemia 8.1 mmol/l, magnesium 1 mmol/l, aspartate aminotransferase 42 U/l, alanine aminotransferase 17 U/l, urea nitrogen 4.6 mmol/l, creatinine enzymatic 46 μmol/l |
| Immunoglobulin (Ig) E 5.2 kIU/l, Vitamin D 25 ng/ml |
| Smear pharynx and nose, and aspirate – normal flora; IgM–mycoplasma pneumoniae – negative titer |

WBC – white blood cells; RBC – red blood cells; PLT – trombocytes

Figure 1. The chest X ray in the posterior anterior position of the 15-month-old boy (on admission)

Figure 2. The multidetector computed tomography at the level of C2–3 vertebral body of the 15-month-old boy (4th hospitalization day) – on the left airway wall (arrow) discovered thickening/hypodense/polypoid change which narrowed asymmetrically the lumen of the border larynx/trachea to the smallest diameter of 2 mm

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