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Application of Flexible Bronchoscopy in the Aetiological Diagnosis of Childhood Refractory Wheezing

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Abstract ***Objective:*** To explore the value of flexible bronchoscopy in aetiological diagnosis of paediatric refractory wheezing. ***Methods:*** A total of 246 patients with refractory wheezing performed flexible bronchoscopy were analysed. They were 146 males and 100 females with a ratio of male to female 1.5:1. Their age ranged from 1 month to 9 years with a median age of 17 months. ***Results:*** Flexible bronchoscopy was performed 269 times. By bronchoscopy, mucus plug was found in 52 patients (21.1%), airway malacia in 76 (30.9%), structural deformity in 32 (13.0%), foreign bodies in 22 (8.9%), tuberculosis in 3 and tumor in one. The aetiology of refractory wheezing varied with different ages. Airway malacia (61.2%) was the main reason in infants, then mucus plug (15.3%). Among toddlers, the most common reason was mucus plug (24.5%), followed by airway malacia (15.1%) and foreign body (14.2%). Bronchoalveolar lavage demonstrated pathogens in 17 (17.3%) of 98 samples. The most common complication was hypoxia during the procedures. They all were transient and alleviated by oxygen supplement or temporary cessation of the procedure. ***Conclusion:*** Flexible bronchoscopy is effective in the aetiological diagnosis of childhood refractory wheezing. Mucus plug, airway malacia, structural deformities and foreign body are the main reasons for childhood refractory wheezing.

Key words Bronchoscopy; Child; Flexible; Wheezing

Introduction

Since flexible bronchoscope was designed by Ikeda et al[1] in 1968, it has been widely accepted and applied by clinicians.[2-5] The main advantages of the flexible fiberoptic bronchoscopy include direct visualisation of the airway lumen up to the fifth generation, as well as the ability to obtain samples from the lower airway for bacteriologic, cytologic, and histologic investigation with minimal risk. In addition to depicting endobronchial abnormalities, the bronchoscopy also allows therapeutic interventions, including removal of mucous plug or foreign body (FB).[6,7] As a consequence, bronchoscopy has now become a mainstay for diagnosis and therapy for respiratory diseases, including those with refractory wheezing. However, as the relatively narrow airway in children, application of flexible bronchoscopy for children was late and limited. Up to now, there is only little information about application of bronchoscopy for the aetiological diagnosis of paediatric refractory wheezing.

Herein, we reported our experiences of the flexible bronchoscopy in the diagnosis of childhood refractory wheezing.

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Materials and Methods

Patient Data

A total of 246 children with refractory wheezing performed flexible bronchoscopy in our hospital from 2006 to 2009 were enrolled. The criteria for refractory wheezing are persistent wheezing for longer than 2 weeks without responsiveness to routine antibiotics or anti-asthma therapy, which included macrolides, beta-Lactam antibiotics, β2-agonist, and corticosteroids. They were 146 males and 100 females. Their age ranged from 1 month to 9 years with a median age of 17 months, including 98 infants (39.8%) younger than one year, 106 toddlers (43.1%) aged from 1 to 3 years, 33 preschool children (13.4%) aged from 3 to 6 years, and 9 school children (3.7%) over 6 years. The duration of wheezing ranged from 2 weeks to 4 months with a mean of 4.1 weeks. Of them, 202 cases (82.1%) had one or two times of similar wheezing history, 96 (39.0%) had a history of eczema, and 18 (7.3%) complicated with congenital heart disease, including atrial septal defect in 2, ventricular septal defect in 10 and patent ductus arteriosus in 6.

Written consent was received from their parents, and this study was approved by the medical ethical committee of Zhejiang University School of Medicine.

Flexible Bronchoscopy

Depending on the age and body weight of the patients, three kinds of fibrobronchoscopes, including Olympus BF-XP40 with 2.8 mm external diameter and 1.2 mm working channel, BF-3C30 (3.6 mm, 1.2 mm) and BF-P40 (4.9 mm, 2.2 mm), were used. Other ancillary equipments included disposable spiral grasping basket type forceps FG (spiral basket type, 3Fr), biopsy forceps FB-56D-1, digital video work station, life monitors, oxygen supply system and emergency equipment.

The flexible bronchoscopy was performed under sedation and local anesthesia after over 6 hours fasting. Diazepam (0.1-0.2 mg/kg) and atropine (0.01-0.02 mg/kg) were administered intramuscularly 20-30 minutes ahead of the operation before 2007, while midazolam (0.1-0.15 mg/kg) was injected 5-10 minutes ahead of the operation since 2007. Aerosolized lidocaine was sprayed on the throat, and then lidocaine was dripped into the trachea and bronchus for local anesthesia during bronchoscopy. The bronchoscope was inserted intranasally unless there was nasal stenosis or hemoptysis which caused difficulty in inserting. For the latter condition, the bronchoscope was inserted through mouth under the protection of a mouth gag. For those with intubation, it was inserted through the endotracheal tube. Spiral grasping basket type forceps or biopsy forceps were used to remove the FB. Adrenaline was administered if necessary. Airway malacia was defined as airway collapse over 1/2 on expiration according to the Chinese guideline of paediatric bronchoscopy (2009 edition) by the Pediatric Bronchoscopy Collaborative Group.[8] Bronchoalveolar lavage (BAL) was performed for microbiological determinations in patients with infection as we previously reported.[9,10]

Heart rate, respiratory rate and pulse oxygen saturation (SpO_2) were monitored during the whole procedure. When the patients were hypoxic (cyanosis, low SpO_2 and/or high heart rate), oxygen of appropriate concentration was given by mask, and the procedure was ceased temporarily when necessary.

Results

Fiberoptic bronchoscopy was performed 269 times in 246 patients with refractory wheezing. Among these patients, most bronchoscopes were inserted intranasally, only 17 (6.9%) were introduced through mouth and 3 (1.2%) were inserted through the endotracheal tube. BAL was performed in 98 patients and endobronchial biopsies in 6. Among 246 patients who received flexible bronchoscopy, cough was noted in all patients, fever in 34 (13.8%), tachypnea in 26 (10.6%), stridor in 5 (2.0%) and hoarseness in 3 (1.2%). The chest X-ray showed bronchiolitis in 74 patients (30.1%), segmental or lobar pneumonia in 32 (13.0%), emphysema in 17 (6.9%), atelectasis in 9 (3.7%). Mediastinum swing was noted in 17 of 41 patients who underwent chest fluoroscopy. Clinically, asthma was diagnosed in 120 (48.8%), bronchiolitis in 51 (20.7%), pneumonia in 30 (12.2%), congenital laryngeal stridor in 23 (9.3%) and bronchial FB in 22 (8.9%), as showed in Table 1.

Under bronchoscopy, mucus plugs (52, 21.1%), airway malacia (76, 30.9%) and structure abnormality (32, 13.0%) were the most common reasons for refractory wheezing. Among 32 patients with structure abnormality, airway constriction or stenosis was found in 15, abnormal origin of bronchial branch in 4 patients, left bronchial dysplasia in 3 and lobar branch dysplasia in 2. Airway FB was found in 22 patients (8.9%), and only 10 had correct diagnosis before bronchoscopy. They were misdiagnosed as asthma in 5 patients, congenital stridor in 3, bronchiolitis in 2 and pneumonia in 2. The less common post-bronchoscopic

diagnoses included bronchial mucosal tuberculosis in 3 (1.2%) and endobronchial neurilemmoma in 1 (0.4%).

Age-related bronchoscopic findings for refractory wheezing was analysed (Table 2). Among infant, airway malacia (60/98, 61.2%) was the main reason, then mucus plug (15/98, 15.3%). In toddlers, the most common reason was mucus plug (26/106, 24.5%) followed by airway malacia (16/106, 15.1%) and FB (15/106, 14.2%). Most of patients with mucus plugs were young children under 3 years (41/52). Airway malacia and structure abnormalities were all found in infants and toddlers younger than 3 years. FB was all found in children less than 6 years.

All BAL samples were sent for microscopic examination, bacteria cultivation, and DNA analysis for *Chlamydiae trachomatis*, *Chlamydia pneumoniae* and *Mycoplasma pneumonia*. BAL detected pathogens in 17 (17.3%) of 98 samples, including 4 *Klebsiella pneumoniae*, 4 *Mycoplasma pneumonia*, 3 *Escherichia coli*, 2 *Chlamydia pneumoniae*, one *Pseudomonas aeruginosa*, 1 *Candida albicans*, 1 Cytomegalic inclusions and 1 *Chlamydiae trachomatis*. Among 6 patients having performed biopsy, 3 samples were confirmed bronchial mucosal tuberculosis, other 2 showed neutrophils infiltration and one showed endobronchial neurilemmoma.

Among 52 patients with mucus plugs, vacuum aspiration and BAL were performed with good outcome. Among 22 patients with airway FB, 19 were removed by flexible bronchoscopy and 3 by rigid bronchoscopy, and all discharged within 3 days. Endobronchial neurilemmoma in one patient was removed by rigid bronchoscopy without recurrence within 2 years. Other 3 patients with bronchial mucosal tuberculosis were referred to special hospital.

During the procedures of these patients, 49.1% (132/269) showed hypoxia. However, they were all transient (<1 min) and alleviated by oxygen supplementation or temporary cessation of the procedure. Small amount of bleeding was found in 7.1% patients (19/269) with good effect of local adrenaline administration. Bradycardia was noted during the procedure in 3 patients. Laryngeal obstruction were noted after bronchoscopy in 3 patients and relieved within 24 hours. No other complications occurred during and after bronchoscopy.

Discussion

Wheezing is a very common symptom in children, especially in infants and preschool children.[11,12] According to Jedrychowski's study, approximately one third of the children experience wheezing in the first 2 years of life.[13] Infantile wheezing also has a close relationship with asthma, and might be the first attack of asthma. However, wheezing is a heterogeneous group and may be caused by many pathological lesions, including intraluminal lesion, airway

Table 1 The clinical and laboratory course of the patient

Pre-bronchoscopic diagnosis	Bronchoscopic findings						
	Mucus plug	Airway malacia	Structural deformity	FB	TB	Tumour	Unknown
Asthma	24	33	11	5	0	1	46
Bronchiolitis	17	15	7	2	0	0	10
Pneumonia	6	8	11	2	1	0	2
Congenital stridor	0	18	2	3	0	0	0
FB	5	2	1	10	2	0	2
Total	52	76	32	22	3	1	60

FB, foreign body; TB, tubercle bacillus

Table 2 Age-related bronchoscopic findings in 246 refractory wheezing children

	Mucus plug	Airway malacia	Structural deformity	FB	TB	Tumour	Unknown
Infant (≤1 year)	15	60	9	5	1	0	8
Toddlers (-3 yeara)	26	16	12	15	1	0	36
Preschool child (-6 years)	9	0	8	2	1	0	13
School child (>6 years)	2	0	3	0	0	1	3
Total	52	76	32	22	3	1	60

FB, foreign body; TB, tubercle bacillus

wall problem and compression from outside the wall. Many auxiliary examinations, including chest roentgenography, computed tomography (CT) scan and magnetic resonance imaging (MRI), might help reveal the reasons and play an important role in the diagnosis and differential diagnosis of childhood wheezing. To date, chest CT and MRI have been used to evaluate a wide spectrum of abnormalities that affect both the airways and the lung. Despite the clarity of anatomic detail that can be obtained with CT and MRI, the precise reason of wheezing in a lot of patients could not be diagnosed. Actually, the real state of trachea and bronchial cavity is much more important in the aetiological diagnosis of wheezing. Bronchoscope made it possible for doctors to get a direct inspection of the airways and provide the opportunity for examination of the underlying pathology.[14]

Herein, we applied flexible bronchoscopy in the aetiological diagnosis of refractory wheezing in 246 patients. Of them, 52 had mucus plugs, mostly occurred in young children under 3 years. These features were consistent with the inflammation and can be caused by infection and allergic reaction as well, including asthma. It is difficult to identify the accurate cause of inflammation in these patients. For the first-attack of wheezing, infection is usually considered and for repeated wheezing, asthma is usually considered. Based on previous studies and this study, BAL and endobronchial biopsies are helpful for the cause and pathogens identification.[10,15,16] In this study, the BAL demonstrated pathogens in 17.3% samples. It may be associated with the fact that viral pathogen is the most common pathogen in young children, but we did not detect viruses in this study. We also noted that most of patients with mucus plugs in our study were less than 3 years. This may be associated with the small caliber of airway and weak cough in young children that make them more easily to develop accumulation of mucus secretion and formation of mucus plug in small airway, resulting in airway partial obstruction and refractory wheezing.[17,18]

It should be taken into account that refractory wheezing can be induced by many other diseases in addition to infection. In our study, airway malacia, structural abnormalities (e.g. abnormal origin of bronchial branch, airway constriction and left bronchial dysplasia), airway FBs, bronchial mucosal tuberculosis and endobronchial tumour were found. Hence, these reasons should be considered in the differential diagnosis of patients with refractory wheezing. Mucus plug, airway malacia, structural deformity and FB should be considered especially in children younger than 3 years. Bronchoscopy should be performed early for diagnosis and therapy in these patients.

Both rigid bronchoscope and flexible bronchoscope can afford a very good vision of airway cavity, but flexible bronchoscope has many advantages. Firstly, the small diameter and flexibility make it possible to access some places where are difficult to reach for rigid bronchoscope, such as grade III or deeper bronchus, left or right upper bronchus and the basal segments of lower bronchus. Secondly, flexible bronchoscopy is more helpful for clearing endogenous FB (e.g. local inflammatory secretion, mucus or blood plug) by vacuum aspiration or BAL, which might be beneficial for the inflammation control and shortening of duration. Especially, BAL can not only wash some small fragment, powdery foreign bodies, or inflammatory section, but also help to investigate pathogens.[19,20] Thirdly, flexible bronchoscopy is suitable for severe wheezing patients, even ICU patients or those with severe complications as in our report and others.[21]

It is notable that only 10 of 22 patients with FB had correct diagnosis before bronchoscopy. Most children were misdiagnosed as asthma, bronchiolitis, congenital stridor or bronchopneumonia. Similar to our previous study, FB was predominant in children under 6 years, especially in young children under 3 years. As their unability to communicate, and the non-specific symptoms of FB aspiration (e.g. paroxysmal coughing, stridor or wheezing) similar to common respiratory infections, it is sometimes very difficult to differentiate. Under such circumstance, early bronchoscopy is helpful[22,23] and flexible bronchoscopy is the preferred choice.[24,25]

Although the flexible bronchoscopy has been widely accepted by paediatrician these years with experiences accumulated,[26] safety of flexible bronchoscopy is a problem of great concern. In our study, we noted that almost 50% patients showed hypoxia during the procedures, which is higher than our previous studied about patients with FB.[8,9] It was also higher than Jones study, which showed that supplemental oxygen was commenced during or immediately after the procedure for 14.4% patients (151/1051).[27] The reasons may be associated with the younger patients in this study, as refractory wheezing was predominated in younger children. Moreover, Jones study also showed that the rate of supplemental oxygen patients was higher in patients with lower FEV1.[27] The another reason is that wheezing pe se means airway narrowing and therefore wheezing children are more vulnerable to hypoxemia and more likely to require supplemental oxygen. Fortunately, we noted that hypoxemia was transient and

alleviated within one min by oxygen supplement or temporary cessation of the procedure. Small amount bleeding was found in 7.1% patients with good effect of local adrenaline administration. Other few complications included transient bradycardia during procedure and laryngeal obstruction after bronchoscopy. No severe complications, such as anesthetic complications, tracheotomy or assisted ventilation, cardiac arrest or large bleeding, were found.

In summary, our results show that flexible bronchoscopy is effective in the aetiological diagnosis of childhood refractory wheezing. Mucus plug, airway malacia, structural deformities and FB are the main reasons for childhood refractory wheezing.

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