



AN 8-MONTH-OLD GIRL WITH SHORTNESS OF BREATH AND WHEEZING

Maarten Blanken, Louis Bont

Wilhelmina Children's Hospital, Utrecht, Division Pediatric Infectious
Diseases

Correspondence: L.Bont@umcutrecht.nl



REASON FOR CONSULTING

An 8-month-old girl was admitted to the emergency department of a secondary hospital for recurrent episodes of shortness of breath. She had been referred to the hospital by the general practitioner after 3 days of gradually worsening symptoms of difficult breathing, cough and expiratory wheeze. No medication had been given.

CLINICAL EXAMINATION

Physical examination on admission showed a well-developed, well-nourished infant. There were no congenital abnormalities. The patient had a normal weight and length.

- Temperature: 38,2°C
- Blood pressure: 90/65 mmHg
- Heart rate: 140/min regular
- Respiratory rate: 65/minute with nasal flaring and intercostal retractions
- Pulse oximetry: 95% on room temperature

She was alert, but dyspneic. The nose contained copious clear mucus. Ear and oropharynx examination showed no inflammation. Lung auscultation revealed a prolonged expiratory phase with end-expiratory wheeze. There were normal heart sounds and no heart murmurs. Further physical examination showed no abnormalities.

On admission she received humidified oxygen by mask and intravenous saline infusion.

MEDICAL HISTORY

She was born at full term by normal vaginal delivery after an uncomplicated gestation. At the age of 7 weeks she experienced a similar period of difficulty breathing. She was then diagnosed with acute bronchiolitis. A nasal aspirate was positive for respiratory syncytial virus (RSV) as determined by



immunofluorescence. Chest radiograph showed hyperexpansion and interstitial markings consistent with bronchiolitis. Bronchoscopy showed normal airway anatomy. She was transferred to the pediatric intensive care unit for 4 days because of continuous hypoxemia (pulse oximeter readings <90%) during the first hours in the hospital. She was mechanically ventilated. Treatment with nebulized salbutamol and ipratropium bromide, did not have a significant effect. After day 2 she improved and after 10 days she was discharged from the hospital. During the following months she experienced 3 relapses of moderate wheeze without the need for hospital admission. There was no family history of heart or lung disease, cystic fibrosis, congenital malformations or other disorders. None of her family members had asthmatic or allergic symptoms.

DIAGNOSTIC APPROACH

This case report represents a common symptom associated with viral respiratory infections of childhood with RSV as the dominant etiologic agent. But are there underlying risk factors for the recurrent episodes described here? Is there a logical explanation for this course of events?

INVESTIGATIONS PERFORMED

Plain chest radiograph (Fig.1) showed normal osseous and soft tissue



structures. No evidence of congenital abnormalities of the pulmonary or cardiac systems was present. The diaphragms had a normal representation on both sides. There was a distinct interstitial haziness visible over all lung fields.

Laboratory test results are shown in Table 1. Besides a slightly elevated leukocyte-count, her lab values are within normal range.



LABORATORY FINDINGS			
WBC	Leuko	17.0	10x9/L
	Neutro	5.40	10x9/L
	Eos	0.46	10x9/L
	Baso	0.08	10x9/L
	Mono	1.04	10x9/L
	Lymfo	10.02	10x9/L
Platelets	420	10x9/L	
Hb	11.0	g/dl	
CRP	4	mg/l	
Total IgE	8	IU/ml	
Other Ig's	No abnormalities		
Capillary Blood gas Analysis			
pH	7.30		
pCO2	50	mmHg	
Bicarbonate	25	Mmol/L	
Base Excess	-3	Meq/L	

A specimen of the nasal secretions was positive for RSV as determined by direct immunofluorescence.

DIFFERENTIAL DIAGNOSIS HYPOTHESES

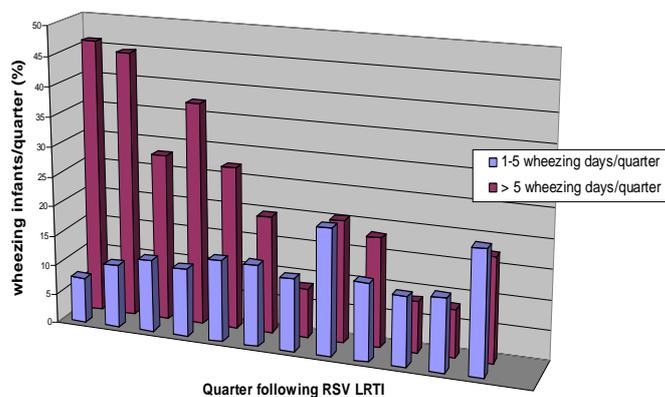
Along with her cough as a sign of general airway irritation, shortness of breath was her major complaint with a clearly audible expiratory wheeze. Wheezing is a symptom of bronchial obstruction caused by malformations, compression, infections or accompanies other pathological processes as a secondary symptom, e.g. aspiration or immunodeficiency. The girl in this case had experienced previous episodes with the same complaints, but not as severe. After exclusion of congenital and other pathological processes, the positive test result of the nasal secretions provides a clear diagnosis of RSV reinfection. But what makes this virus so pathogenic every time it reappears in the winter season?

SYNTHESIS AND CONCLUSION

Bronchiolitis is a common illness affecting young children. It is primarily a disease with respiratory distress, crepitation and expiratory wheeze associated with respiratory viral infections, including RSV, rhinovirus and



parainfluenza viruses. RSV is one of the most important respiratory pathogens in infancy causing the majority of lower respiratory tract infections during the winter season. Almost all young children experience RSV infection at least once in the first two years of life, and >65% become infected during their first year, with the peak incidence for lower respiratory disease occurring between 2 and 7 months of age (1, 2). Hospitalization rates for RSV illness are 5-20 cases per 1000 infants <1 year of age (3, 4, 5). Mechanical ventilation is required in 7-21% of hospitalized infants with RSV bronchiolitis, with lower gestational age, requirement of neonatal oxygen supplementation and bronchopulmonary dysplasia as significant risk factors (6, 7, 8). Mortality in RSV-infected infants with lower respiratory tract symptoms is <1% (9). Reinfection with RSV occurs frequently and usually has a mild character with symptoms of uncomplicated upper respiratory tract infection (10). However, in our case RSV reinfection had caused the severe wheezing episode. Post-bronchiolitis wheeze occurs in about 42–71% of cases of RSV bronchiolitis. Post-bronchiolitis wheeze is characterized by recurrent episodes of wheeze during pre-school years (Fig.2).



Most epidemiological studies do not find an association between post-bronchiolitis wheeze and the development of allergic asthma, although this issue is subject to debate in literature.

Figure 2 Number of days with respiratory wheeze per quarter following RSV LRTI. Parents recorded daily respiratory symptoms which were analysed per quarter. Infrequent wheeze (1-5 days/quarter) and frequent wheeze (>5 days/quarter) are distinguished. Data from Thorax. 2004Jun; 59(6):512-6



It is generally assumed that wheezing episodes following RSV LRTI are associated with viral upper respiratory tract infections and not allergen exposure, in contrast to children who suffer allergic asthma (11).

The pathogenesis of post bronchiolitis wheeze is not fully understood. Is it the virus-induced pathogenic effect on the airway epithelium which leaves these children with vulnerable lungs and wheezing episodes (serial hypothesis)? Or are these children born with small or vulnerable airways making them susceptible for both viral infections and wheezing episodes (parallel hypothesis)? This serial versus parallel hypothesis (Fig.3) is an important challenge in the attempts to understand the pathogenesis of post-bronchiolitis wheeze. Pre-existent morbidity has been shown to be a factor. The risk of having a wheezing illness is almost 4 times higher in children with pre-existent lung function abnormalities. The children whose initial values for lung volume at the end of tidal expiration were in the lowest third, even had an 10-16 fold increased risk (12). There is also evidence that several genetic phenotypes are of influence to disease severity and post-bronchiolitis symptoms. It was shown that disease severity is associated with a common single nucleotide polymorphism close to the IL-8 gene and an increased IL-8 production upon stimulation (13). Another such polymorphism has recently been found which clearly depicts early post-bronchiolitis wheezing and wheezing later in childhood as distinct pathophysiological entities. We found a significant overrepresentation of an IL-13 polymorphism in children with late wheezing, but this polymorphism was not associated with severe RSV LRTI (unpublished data). As such, these results support the concept that mechanisms underlying the development of severe RSV LRTI are to be studied separately from the pathophysiology of wheezing illness.

In addition to pre-existent factors, the immune response seems to be the major contributor to disease severity as is demonstrated in several studies. Especially in early infancy the immune system doesn't seem able to elicit an appropriate Th1 immune response against the invading virus. Kristjansson found a local Th2 response and signs of eosinophils activation due to an elevated production of the Th2-type cytokine IL-4 (14).

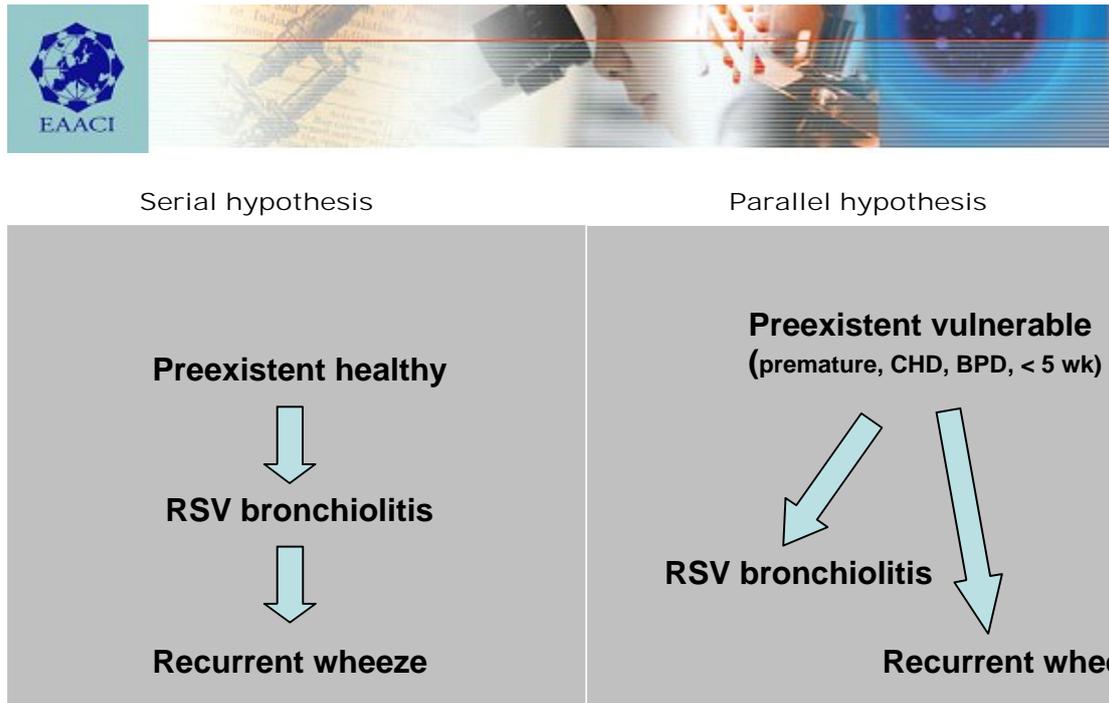


Figure 3 Pathogenesis of post-bronchiolitis wheeze: serial vs. parallel hypothesis.

TREATMENT

The treatment possibilities for RSV infection are very limited. An attempt to prevent RSV infection using formalin-inactivated RSV became a disastrous event, but researchers continue their search for a safe and effective vaccine. High-risk children can be given prophylaxis, by monthly administration of a monoclonal antibody against the RSV F-protein (passive immunization). Especially high-risk children who are younger than 6 months of age at the start of the RSV season should receive this therapy. Because of high costs, this type of prophylaxis can not be used for all infants.

Several therapies, including ribavirin, bronchodilators, racemic epinephrine and corticosteroids are not recommended as standard therapies because of lack of benefit found in RCTs. In two different longitudinal studies intermittent inhaled corticosteroid therapy had no effect on the short- or long term benefit and had no disease modifying effect after the therapy was discontinued. There was also no significant difference between corticosteroid and control groups in the development of persistent wheezing (15, 16). Recently, Lehtinen and colleagues found that systemic steroids during the first episode of wheezing prevented post-bronchiolitis wheeze, but only when the initial bronchiolitic episode was caused by rhinovirus, and not by RSV (17). Use of montelukast, a leukotriene receptor antagonist, during RSV infection is



another therapy which has been suggested to post-bronchiolitis wheeze. However, this study needs to be confirmed before it can be accepted as standard treatment. Taken together, there is no effective treatment for RSV bronchiolitis or an intervention that effectively prevents post-bronchiolitic symptoms.



References

- (1) Parrott, R. H., H. W. Kim, J. O. Arrobio, D. S. Hodes, B. R. Murphy, C. D. Brandt, E. Camargo, and R. M. Chanock. 1973. Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease with respect to age, immunologic status, race and sex. *Am. J. Epidemiol.* 98:289.
 - (2) Glezen, W. P., L. H. Taber, A. L. Frank, and J. A. Kasel. 1986. Risk of primary infection and reinfection with respiratory syncytial virus. *Am. J. Dis. Child* 140:543.
 - (3) Karron, R. A., R. J. Singleton, L. Bulkow, A. Parkinson, D. Kruse, I. DeSmet, C. Indorf, K. M. Petersen, D. Leombruno, D. Hurlburt, M. Santosham, and L. H. Harrison. 1999. Severe respiratory syncytial virus disease in Alaska native children. RSV Alaska Study Group. *J. Infect. Dis.* 180:41.
 - (4) Shay, D. K., R. C. Holman, R. D. Newman, L. L. Liu, J. W. Stout, and L. J. Anderson. 1999. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA* 282:1440.
 - (5) Glezen, W. P. 2004. The changing epidemiology of respiratory syncytial virus and influenza: impetus for new control measures. *Pediatr. Infect. Dis. J.* 23:S202-S206.
 - (6) Frankel, L. R., N. J. Lewiston, D. W. Smith, and D. K. Stevenson. 1986. Clinical observations on mechanical ventilation for respiratory failure in bronchiolitis. *Pediatr. Pulmonol.* 2:307.
 - (7) Tissing, W. J., H. A. van Steensel-Moll, and M. Offringa. 1993. Risk factors for mechanical ventilation in respiratory syncytial virus infection. *Eur. J. Pediatr.* 152:125.
 - (8) Flamant, C., F. Hallalel, P. Nolent, J. Y. Chevalier, and S. Renolleau. 2005. Severe respiratory syncytial virus bronchiolitis in children: from short mechanical ventilation to extracorporeal membrane oxygenation. *Eur. J. Pediatr.* 164:93.
 - (9) Thompson, W. W., D. K. Shay, E. Weintraub, L. Brammer, N. Cox, L. J. Anderson, and K. Fukuda. 2003. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 289:179.
 - (10) Henderson, F. W., A. M. Collier, W. A. Clyde, Jr., and F. W. Denny. 1979. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. *N. Engl. J. Med.* 300:530.
 - (11) Pullan, C. R., and E. N. Hey. 1982. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br. Med. J. (Clin. Res. Ed)* 284:1665.
 - (12) Martinez, F. D., W. J. Morgan, A. L. Wright, C. J. Holberg, and L. M. Taussig. 1988. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N. Engl. J. Med.* 319:1112.
 - (13) Hull, J., A. Thomson, and D. Kwiatkowski. 2000. Association of respiratory syncytial virus bronchiolitis with the interleukin 8 gene region in UK families. *Thorax* 55:1023.
 - (14) Kristjansson, S., S. P. Bjarnarson, G. Wennergren, A. H. Palsdottir, T. Arnadottir, A. Haraldsson, and I. Jonsdottir. 2005. Respiratory syncytial virus and other respiratory viruses during the first 3 months of life promote a local TH2-like response. *J. Allergy Clin. Immunol.* 116:805.
 - (15) Guilbert, T. W., W. J. Morgan, R. S. Zeiger, D. T. Mauger, S. J. Boehmer, S. J. Szeffler, L. B. Bacharier, R. F. Lemanske, Jr., R. C. Strunk, D. B. Allen, G. R. Bloomberg, G. Heldt, M. Krawiec, G. Larsen, A. H. Liu, V. M. Chinchilli, C. A. Sorkness, L. M. Taussig, and F. D. Martinez. 2006. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N. Engl. J. Med.* 354:1985.
 - (16) Bisgaard, H., M. N. Hermansen, L. Loland, L. B. Halkjaer, and F. Buchvald. 2006. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N. Engl. J. Med.* 354:1998.
 - (17) Lehtinen, P., A. Ruohola, T. Vanto, T. Vuorinen, O. Ruuskanen, and T. Jartti. 2006. Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. *J. Allergy Clin. Immunol.*
-



Summary

We have described an infant with recurrent episodes of wheeze following RSV bronchiolitis. Pre-existent as well as virus-induced pathophysiological mechanisms have been discussed. It remains a challenge to identify children with persistent asthma among those who experience post-bronchiolitis wheeze. To date, no single treatment has convincingly been shown to be effective. The precise underlying mechanisms of post-bronchiolitis wheeze need to be unraveled before safe and effective preventive and treatment strategies can be developed.
