

Short Communication

Relationship between Lower Respiratory Tract Infections Caused by Respiratory Syncytial Virus and Subsequent Development of Asthma in Japanese Children

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SUMMARY: Several studies in Western countries have found that lower respiratory tract infections (LRTIs) caused by the respiratory syncytial virus (RSV) in infancy may subsequently trigger the development of asthma. In this study, we enrolled 262 infants under the age of 3 who had been admitted to our hospital with LRTI between September 2002 and August 2003. RSV infection was diagnosed in these patients using an RSV rapid diagnostic kit and by measuring antibody titers in paired serum samples. In March 2009, we sent questionnaires on post-discharge allergic conditions to the families of the 249 patients, excluding 13 who had a prior history of asthma. A total of 133 responses were received (response rate, 53.4%); RSV was detected in 36 patients of the RSV group and 97 patients of the non-RSV group. Wheezing was experienced post-discharge by 10 patients in the RSV group (27.8%) and 32 in the non-RSV group (33.0%) ($P = 0.57$). Four patients in the RSV group (11.1%) and 6 in the non-RSV group (6.2%) ($P = 0.34$) were treated for asthma. This study revealed that RSV LRTI in infancy does not predispose children to subsequent development of asthma at the age of 7 years and 7 months. We believe that this is the first Japanese survey that has examined the relationship between RSV LRTI in infancy and the subsequent development of asthma.

Respiratory syncytial virus (RSV) is the main cause of lower respiratory tract infections (LRTIs) in infants. Almost all children are infected with RSV before they are 2 years old. Those at high risk include premature infants and children with bronchopulmonary dysplasia or congenital heart defects, but RSV infections in healthy infants can also be serious enough to necessitate hospitalization (1,2). Children with RSV LRTI admitted to hospitals show airway hyper-responsiveness and are known to subsequently experience recurrent bouts of wheezing. Numerous studies have examined the relationship between RSV infections and the onset of recurrent wheezing and asthma and have suggested that RSV LRTIs may be a risk factor for asthma (3–11). However, most of these studies have been conducted in Western countries. Little is known about the risk factors for asthma in cases of Asian children, and significant international variations have been reported in the prevalence of asthma (12). The purpose of this study was to examine the relationship between RSV LRTI and the subsequent development of asthma in Japanese children.

We previously conducted a prospective survey of 262 children with LRTI, who were under the age of 3 years and had been admitted to our pediatric department. The

study was carried out from September 1, 2002 to August 31, 2003, in order to determine whether the 262 children with LRTI were infected with RSV (13). At the time of admission we collected nasal washing samples from the patients for antigen detection using the RSV rapid diagnostic kit (RSV Examan; Nippon Becton Dickinson Co., Tokyo, Japan). We also collected paired serum samples during and after the admission for measuring antibody titers using the complement fixation assay (SRL, Inc., Tokyo, Japan). Of the 262 patients, 66 were either positive for viral antigen or they showed seroconversion or a fourfold increase in the antibody titer, and these patients were designated as the RSV group (positive for RSV infection); the remaining 196 patients were designated as the non-RSV group. None of the patients from either of the groups were administered palivizumab.

In March 2009, we administered questionnaires to the families of the 249 patients, excluding 13 patients with a history of asthma before admission. The questionnaires sought information on allergic conditions in the patients after their discharge from the hospital; it included questions on symptoms of wheezing, allergic conditions (asthma, atopic dermatitis, urticaria, and allergic rhinitis), and a family history of these conditions, and a history of RSV infections. Patients were considered as having a history of asthma if they had been diagnosed with asthma and treated by a physician. This survey was approved by the Konan Kosei Hospital Institutional Review Board.

Statistical analyses were performed using Fisher's direct probability test and the t test; $P < 0.05$ was consi-

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Table 1. Background factors for RSV and non-RSV groups

	RSV group (<i>n</i> = 36)		Non-RSV group (<i>n</i> = 97)		<i>P</i> value
Age at time of admission (months)	20.0 ± 9.7		17.2 ± 9.4		0.13
Gender					0.60
Male	22	61.1%	64	66.0%	
Female	14	38.9%	33	34.0%	
Gestation (weeks)	38.6 ± 2.5		38.6 ± 1.7		0.95
Birth weight (g)	3,100 ± 587		3,008 ± 423		0.32
Smoker in family	14	38.9%	49	50.5%	0.23
Family pet	12	33.3%	30	30.9%	0.79
Family history of asthma (duplication possible)					
Father	4	11.1%	5	5.2%	0.22
Mother	3	8.3%	3	3.1%	0.20
Sibling	2	5.6%	9	9.3%	0.49
Family history of atopic dermatitis (duplication possible)					
Father	3	8.3%	7	7.2%	0.83
Mother	5	13.9%	7	7.2%	0.23
Sibling	6	16.7%	7	7.2%	0.10
Family history of atopic rhinitis (duplication possible)					
Father	18	50.0%	48	49.5%	0.96
Mother	18	50.0%	48	49.5%	0.96
Sibling	12	33.3%	23	23.7%	0.26

Table 2. History of allergic conditions in RSV and non-RSV groups

	RSV group (<i>n</i> = 36)		Non-RSV group (<i>n</i> = 97)		RR	95% CI
Asthma						
Past history	5	13.9%	12	12.4%	1.12	0.43–2.96
Under treatment	4	11.1%	6	6.2%	1.80	0.54–6.00
Wheezing						
(detected by physician)						
≥ 3 times	6	16.7%	17	17.5%	0.95	0.41–2.22
1–2 times	4	11.1%	11	11.3%	0.98	0.33–2.88
Wheezing						
(detected by parents)						
≥ 3 times	7	19.4%	19	19.6%	0.99	0.46–2.16
1–2 times	3	8.3%	13	13.4%	0.62	0.19–2.06
Atopic dermatitis	6	16.7%	15	15.5%	1.08	0.45–2.56
Urticaria	10	27.8%	20	20.6%	1.35	0.69–2.60
Allergic rhinitis	17	47.2%	34	35.1%	1.35	0.87–2.09

RR, relative risk; CI, confidence interval.

dered significant. We estimated the values for the relative risk (RR) of developing asthma, wheezing, or other allergic conditions, and their 95% confidence intervals (CIs).

Responses were received from the families of 133 (53.4%) of 249 patients; the response rate was 57.1% in the case of the RSV group (*n* = 63) and 52.2% in the case of the non-RSV group (*n* = 186) (*P* = 0.49). The average age of the patients when the responses were received was 7 years and 7 months. Of the 133 respondents, 36 belonged to the RSV group and 97 to the non-RSV group. The average time interval between admission for LRTI and response to the questionnaire was 6.1 ± 0.3 years, and the average age of the patients at the time of admission was 20.0 ± 9.7 months in the RSV group and 17.2 ± 9.4 months in the non-RSV group (*P* = 0.13). No significant differences were observed

between the two groups with respect to any of the background factors that were examined, including family history of allergic conditions (Table 1). None of the patients were infected with RSV after discharge from the hospital.

Five patients in the RSV group (13.9%) and 12 in the non-RSV group (12.4%) had a history of asthma (*P* = 0.82, RR = 1.12, 95% CI = 0.43–2.96), and 4 patients in the RSV group (11.1%) and 6 in the non-RSV group (6.2%) were on a regular treatment for asthma (*P* = 0.34, RR = 1.80, 95% CI = 0.54–6.00). Wheezing was noted in 10 (27.8%) patients in the RSV group and 32 (33.0%) patients in the non-RSV group (*P* = 0.57, RR = 0.84, 95% CI = 0.46–1.53). No significant differences were observed between the two groups in terms of occurrence of asthma or wheezing. There were no differences in the two groups with regards to the

presence of atopic dermatitis, urticaria, or allergic rhinitis (Table 2).

Many studies, mainly in Western countries, have examined the relationship between RSV infections in infancy and the subsequent development of asthma (3–11). Sigurs et al. (3–5) conducted a prospective survey of 47 infants hospitalized for RSV bronchiolitis and 93 control individuals under the age of 13 years. They found that the number of asthma patients in the RSV group was higher than that in the control group. A prospective survey by Stein et al. (6) found that the group who acquired RSV LRTI before the age of 3 years had a significantly higher risk of recurrent wheezing at the age of 6 (RR = 4.3, CI = 2.2–8.7); however, the risk subsequently decreased with age, until there was no difference at age 13. Singleton et al. (7) compared 204 children hospitalized for RSV infections with 338 control groups and found significant correlations between hospital admissions in the RSV group and wheezing attacks up to the age of 4, and between LRTI and the diagnosis of asthma; the degree of correlation declined with age until there was no difference after the age of 5. Henderson et al. (8) studied a group of 150 children (1.1% of the cohort) hospitalized for RSV bronchiolitis and a control group, and found that 38.4% of the RSV group were diagnosed with asthma by the age of 7 years and 7 months, which is significantly higher than the percentage of the non-RSV group (20.1%) who were diagnosed with asthma (odds ratio [OR] = 2.5, CI = 1.4–4.3). At the age of 6 years and 9 months, no difference was observed between the two groups with respect to the incidence of ≥ 5 wheezing episodes per year. Bont et al. (9) studied 140 children who had RSV LRTI at 3-month intervals until the age of 3 and reported frequent wheezing (> 5 days/3 months) in 50% of the patients at first, which then decreased to 30% in the second year after birth, and 10% before the third year. These studies differ with respect to the time of occurrence and the severity of the RSV infections, but they showed that risk of wheezing following an RSV infection tends to decrease with age.

This study does not provide any evidence that RSV LRTI in infancy predisposes children to the subsequent development of asthma at the age of 7 years and 7 months. To our knowledge, ours is the first Japanese survey to examine the relationship between RSV LRTI in infancy and the subsequent development of asthma in Japan. The incidence of asthma varies across countries, suggesting that racial differences and environmental factors are important in the development of asthma in childhood (12). Our results indicate that RSV infections in Japanese children may not be associated with subsequent development of asthma later in life. On the other hand, the possibility that the non-RSV group could include LRTI patients with infections due to other pathogens such as rhinovirus, human metapneumovirus, and parainfluenza virus was undeniable. In particular, rhinovirus, like RSV, has been reported to be an LRTI pathogen and a risk factor for subsequent development of asthma (15). Furthermore, studies performed in

other countries have indicated that the risk of wheezing after RSV infection tends to decrease with age. The patients in the present study were older than those in the previous studies, which may explain why no difference was noted in the risk for developing wheezing between the RSV group and the non-RSV group. We divided our patients into three age groups: < 6 months ($n = 16$), 6–12 months ($n = 35$), > 12 months ($n = 82$) and compared the RSV and non-RSV groups. No significant difference was observed between the two groups with respect to the prevalence of asthma (data not shown), which may be attributed to the small number of study participants being compared. Further studies with a larger number of Japanese children are required to validate our findings.

Conflict of interest None to declare.

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