INTERNAL MEDICINE

□ CASE REPORT □

Non-localized *Mycobacterium avium* Lung Disease Successfully Treated with Lobectomy and Chemotherapy

Noboru Hamada, Noriko Kawata, Takuo Shibayama, Shigeki Makihara, Atsuhiko Tada, Ryo Soda and Kiyoshi Takahashi

Abstract

A 17-year-old boy presented with a large cavity and bilateral nodular opacities on his chest roentgenogram. *Mycobacterium avium* was identified in his sputum. According to the recommendations of the American Thoracic Society, he was not strongly recommended to undergo surgery because of non-localized lesions. But since cavities can provide a means for disease to spread to other lobes, we decided to perform a lobectomy including the cavity combined with chemotherapy. Now he has been well for 4 years without exacerbation. There is a possibility of long-term remission with this combination treatment in cases a destructive lesion of airway such as a cavity which is localized to one lobe, even if other lesions such as nodular opacities exist in many other lobes.

Key words: *Mycobacterium avium*, non-localized lesion, lobectomy, chemotherapy

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Introduction

Pulmonary resection for *Mycobacterium avium* lung disease continues to play an important role when the disease has not been successfully treated by chemotherapy alone (1). However, the indication and the timing of pulmonary resection are still problematic, and to date there are no adequate recommendations. Here, we report a rare case of a young immunocompetent boy with bilateral and multiple lobar lesions of *Mycobacterium avium* successfully treated with chemotherapy before and after lobectomy with some literature review.

Case Report

A 17-year-old immunocompetent boy presented with a 1-month history of cough, fever and an abnormal chest roentgenogram (Fig. 1A). A computed tomographic (CT) scan revealed a large cavity lesion in the right upper lobe and multiple small centrilobular nodular opacities not only in the other right lobes, but also in the left lung (Fig. 1B). The smears and cultures of three separate expectorated sputums were positive for acid-fast bacilli, and *Mycobacterium avium* was identified using the polymerase chain reaction (PCR). Minimal inhibitory concentrations (MICs) of various antituberculous drugs against this strain were determined by using a broth microdilution method. The MICs of rifampisin, clarithromycin, ethambutol and streptomycin were 0.125 μg/mL, 0.5 μg/mL, 8 μg/mL and 8 μg/mL, respectively. According to these data, he fulfilled the clinical, radiologic and microbiological criteria of the American Thoracic Society (ATS) for nontuberculous mycobacteria (2). The results of laboratory tests, including a CBC count and quantitative immunoglobulin G, A, and M levels were normal and anti-HIV antibody was negative and tuberculin skin test was positive (Table 1). He had neither physical findings nor a previous history of sinusitis to rule-out cilia dysfunction and no hot tub exposure. He was initially treated with ethambutol at 750 mg/day, and rifampisin at 450 mg/day, and clarithromycin at 600 mg/day, and streptomycin at 500 mg every other day. By the time of hospital discharge, 6 months after the start of treatment, his subjective symptoms were improved and the cultures of his sputum became negative for acid-fast bacilli. But the cavity in the right upper lobe and other centrilobular nodular opacities in other lobes still existed. We

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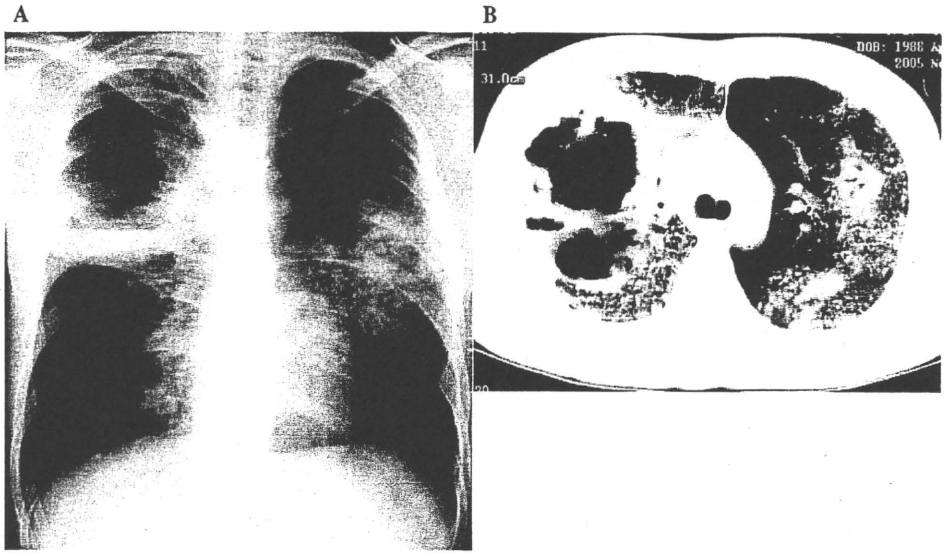

Figure 1. A chest roentgenogram (A) and computed tomography scan (CT) (B) reveal a cavity in the right upper lobe and bilateral multiple small centrilobular nodular opacities in not only the other right lobes, but also all the left lobes.

Table 1. Laboratory Findings on Admission

Hematology			Blood chemistry		
WBC	4900	/μL	AST	31	U/L
Neu	65.9	%	ALT	28	U/L
Lym	18.1	%	LDH	430	IU/L
Eos	3.1	%	ALP	153	IU/L
Baso	0.7	%	BUN	16	mg/dL
Mono	12.2	%	Cr	0.8	mg/dL
RBC	445	$\times 10^4$/μL	Na	137	mEq/L
Hb	13.6	g/dL	K	3.6	mEq/L
Ht	39.9	%	Cl	102	mEq/L
Plt	18.1	$\times 10^4$/ μL	FBG	97	mg/dL
			HbA1c	4.8	%
Serology					
CRP	4.23	mg/dL	Virus marker		
ESR 60'	50	mm	HBs Ag	(-)	
IgG	1255	mg/dL	HCV Ab	(-)	
IgA	347	mg/dL	CMV ab	(-)	
IgM	65	mg/dL	HIV Ab	(-)	
RF	<5	IU/mL			
ANA	(-)		Tuberculin skin test		
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thought that it was difficult to completely eradicate the *Mycobacterium avium* in the cavity by chemotherapy alone, and residual *Mycobacterium avium* in the cavity were capable of spreading to the other lobes again. Thus, he underwent a right upper lobectomy including the cavity. No major postoperative complications occurred. Surgical specimen of the right upper lobe demonstrated granulomatous inflammation with caseating necrosis, and direct microscopic examination for acid-fast bacilli was positive. We thought that the decision of lobectomy was appropriate, in order to prevent spreading the *Mycobacterium avium* from the cavity to the other lobes. Then a combination chemotherapy including ethambutol, rifampisin, and clarithromycin were performed for more than one year after the lobectomy. When he finished his treatment, the bilateral multiple residual centrilobular nodular opacities of the lungs were all resolved on his chest high resolution CT scan (Fig. 2A) and he has been well for 4 years without exacerbation (Fig. 2B).

Discussion

Mycobacterium avium lung disease was initially described as a cavitary disease of the upper lobe in elderly and man smokers who had disruption of local host defense (3). On the other hand, many cases have been recently reported in middle-aged to elderly non-smoking women without obstructive lung disease (4). It is very rare that a young and immunocompetent boy would suffer from non-localized *Mycobacterium avium* lung disease. In an analysis of 706 patients infected with *Mycobacterium intracellulare-avium*

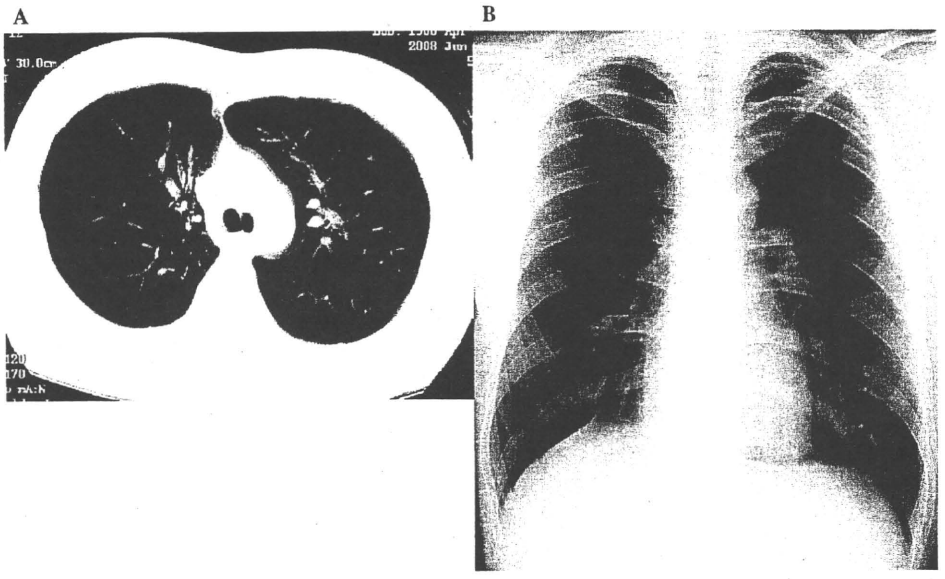

Figure 2. A chest CT (A) and roentgenogram (B) taken at the end of his treatment reveal that the cavity and the other multiple centrilobular nodular opacities have almost disappeared.

complex in Texas from 1967 to 1976, Ahn et al reported that about 2% of the patients were less than 20 years old (5). A young boy can suffer from *Mycobacterium avium* lung disease when he is an immunocompromised host or his local host defense of the respiratory tract is widely destructive, such as that seen in cystic fibrosis or bronchiectasia (6). However, the present patient had no abnormalities in his immunological examinations and his old chest roentgenogram, and so we were unable to clarify the cause of the attack.

Combination chemotherapy regimens including newer macrolides for *Mycobacterium avium* lung disease are more effective than the earlier regimens without newer macrolides. But the success rates of these combination chemotherapy regimens have peaked at 72-82%. Failure rates are still high and relapse may occur after seemingly successful therapy (7). Therefore, there are still some patients with *Mycobacterium avium* lung disease whose disease was not controlled by chemotherapy alone.

On the other hand, The American Thoracic Society has developed specific recommendations for the pulmonary resection of *Mycobacterium avium* lung disease. Patients whose disease is localized to one lung and who can tolerate resectional surgery might also be considered for pulmonary resection, if there has been a poor response to drug therapy or if the patient's isolate has become macrolide-resistant (2). The present patient revealed a cavity in the right upper lobe and multiple nodular opacities of all other lobes bilaterally. According to the recommendations of the American Thoracic Society for the surgical treatment of *Mycobacterium avium* lung disease (2), he was not strongly recommended to undergo a pulmonary resection. Nevertheless, we chose pulmonary resection including the cavity because we thought it would be difficult for chemotherapy alone to eradicate the *Mycobacterium avium* in the cavity completely. Lynch et al reported that a high percentage of positive sputum cultures were obtained from air space disease or cavity (8). Rosenzweig reported that the bacteriologic response for chemotherapy was found to be related to the presence of a cavity, as well as the radiographic extent of disease from the analysis of 100 cases of pulmonary mycobacterium intracellulare-avium complex infection during about 3 years (9). Takada et al also reported that patients with short-term follow up may respond to chemotherapy, whereas those with longstanding disease may show slow progression from the analysis of 50 cases of pulmonary nontuberculous mycobacterial infection during about 5 years (10). Thus, the cavity with the residual *Mycobacterium avium* would keep providing a means for disease to spread to the other lobes through the bronchi (11). Because we had to prevent disease progression continuously in this young boy for his remaining long life, we decided to add pulmonary resection to the chemotherapy despite the some response to the chemotherapy. And his subjective symptoms actually did improve and the shadow of his chest roentgenogram almost disappeared with this combination treatment.

We think that there is a possibility of long-term remission and survival with this combination treatment under the following two conditions: 1) even if *Mycobacterium avium* lung lesions exist in many lobes, a destructive lesion of the airway such as a cavity is localized to one lobe, and 2) the patient has good response to drug therapy.

Further studies are needed to clarify whether our recommendation is useful or not for non-localized *Mycobacterium avium* lung disease.

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Desert Dust Exposure Is Associated with Increased Risk of Asthma Hospitalization in Children

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Rationale: **Desert dust particles, including quartz, which causes inflammatory responses in the airway in animal studies, are transported to widespread regions around the globe. Epidemiologically, areas impacted by desert dust storms, such as communities in the Middle East and the Caribbean, seem to have higher incidences of asthma than might be expected.**

Objectives: **We investigated the magnitude of association between airborne mineral dust concentration and hospitalization of children for asthma exacerbation by using Light Detection And Ranging (LIDAR) with a polarization analyzer for an exposure measurement, which can distinguish mineral dust particles from other particles.**

Methods: **A case-crossover design was used. The exposure measurement was LIDAR's nonspherical extinction coefficient. The outcome measurement was hospitalization of children aged 1 to 15 years for asthma exacerbation in eight principal hospitals in Toyama, a local area in Japan bordering the Japan Sea, during February to April, 2005 to 2009.**

Measurements and Main Results: **During the study period, there were 620 admissions for asthma exacerbation, and 6 days with a heavy dust event (daily mineral dust concentration > 0.1 mg/m^3). Conditional logistic regression showed a statistically significant association between asthma hospitalization and a heavy dust event. The crude odds ratio (OR) of the heavy dust event for hospitalization on the day was 1.88 (95% confidence interval [CI], 1.04–3.41; P = 0.037), and the OR of heavy dust event during the previous week was 1.83 (95% CI, 1.31–2.56; P = 0.00043). The OR adjusted by other air pollutant levels, pollen, and meteorological factors was 1.71 (95% CI, 1.18–2.48; P = 0.0050).**

Conclusions: **Heavy dust events are associated with an increased risk of hospitalizations for asthma.**

Keywords: Asian dust; Kosa; mineral dust; African dust; quartz

Aerosol particles are produced by a variety of processes, both natural and anthropogenic. Among them, desert dust constitutes about 40% of the aerosol mass injected into the troposphere (1).

Quartz, an amorphous and crystalline silica, included in dust sand, is known to cause respiratory disease in occupationally exposed people and highly exposed people who live close to deserts (2–5). It causes inflammatory responses with the release of inflammatory cytokines in the lungs of rats in experimental studies (6–8).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Desert dust particles, including quartz, which cause inflammatory responses in the airway in animal studies are transported to widespread regions around the globe. However, no studies have investigated the magnitude of desert dust effects on asthma exacerbation with quantitative objective measures of desert dust in the air.

What This Study Adds to the Field

Desert dust exposure was associated with the increased risk of asthma hospitalization for children with asthma. The risk was particularly high for boys.

Desert dust is transported to wide regions of the world. Dust originating from the Sahara desert can be transported across the Atlantic Ocean and reach northeastern South America, the Caribbean, Central America, and southeastern United States (9). Dust originating from the Taklimakan desert was transported more than one full circle around the globe in about 13 days (10). Epidemiologically, areas impacted by desert dust storms, such as communities in the Middle East and the Caribbean, seem to have higher incidences of asthma than might be expected (2, 11–13). Although several clinical studies tried to relate desert dust to asthma, none had a quantitative objective measure of desert dust in the air (14–19) except one that measured the amount of some minerals in the air (20). On the other hand, extensive studies of the atmospheric aerosol particle load in the troposphere have been conducted in the last decades using the Light Detection and Ranging (LIDAR) technique in North America, Western Europe, and Asia (10, 21–27). LIDAR is an optical remote sensing technology that measures properties of scattered light to find range and/or other information on a distant target. The LIDAR system with a polarization analyzer can distinguish mineral dust particles (nonspherical particles) from non–mineral dust particles (spherical particles) (28–32). Although particulate matter 2.5 μm or smaller in size and particulate matter 10 μm or smaller in size differentiate the size of particles but do not differentiate mineral dust from nonmineral dust, the LIDAR system with a polarization analyzer does not differentiate the size of particles but does differentiate the shape of particles. Thus, the LIDAR system can specifically measure quantity of mineral dust. In Asia, observations of tropospheric aerosol particles are continuously being conducted using a network of LIDARs at 23 locations in Japan, Korea, and China.

The present study took place in Toyama, Japan, a local prefecture occasionally susceptible to Asian dust events in the spring. Asian dust is a windblown dust originating from the

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deserts of Mongolia and China. It is a seasonal event, and Asian cities experience yellowish air on several days in the spring when the dust is blowing. We investigated the magnitude of the effect of mineral dust particles on children's asthma exacerbation using the LIDAR measurement. The primary hypothesis was that heavy dust events are associated with an increased risk of hospitalizations for asthma.

METHODS

Study Design

The present study used a case-crossover design (33–35). Four controls were matched to each hospitalization, ± 2 weeks and ± 4 weeks. The study protocol was approved by the Human Research Protection Program of the University of California, San Diego.

Hospitalization Data

Data were obtained from the hospitalization records of eight principal hospitals in Toyama, Japan. Potential cases were children aged 1 to 15 years who had at least one hospitalization with the admission diagnosis of asthma in any of the eight principal hospitals in Toyama between February and April, from 2005 to 2009. Hospitalization referred to actual inpatient admission and did not include emergency visits that did not end in admission.

Dust, Air Pollution, and Meteorological Data

The mineral dust data were based on measurement by the LIDAR system with a polarization analyzer (10, 28, 36).

A heavy dust event day *a priori* was defined as the day when the daily (24 h) average dust extinction coefficient in Toyama, measured by LIDAR less than 1 km height from the ground, recorded more than 0.1/km, which corresponded to 0.1 mg/m^3 mineral dust particles, the standard threshold for particulate matter (28, 36).

Statistical Analysis

Initially, a conditional logistic regression analysis was performed using hospitalization as the dependent variable, and heavy dust event as the independent variable changing the hazard/control period from 1 to 7 days to determine the crude odds ratio (OR) of heavy dust events for asthma hospitalization. We examined possible climatic confounders (daily average temperature, temperature difference from the previous day, temperature difference within the day, air pressure, air pressure difference from the previous day, humidity, and wind speed) if each had an increased OR for asthma hospitalization with various cut-off values and various lag structures up to lag 0 to 6 (Days 0–6). Then we performed cross-correlations of the variables and conducted a conditional logistic regression to determine the climatically adjusted OR using hospitalization as the dependent variable and, as independent variables, heavy dust event and all climatic variables that showed apparent increase ($P < 0.1$) of OR for asthma hospitalization among the above. We examined other air pollutants (gaseous NO_2, SO_2, and photochemical oxidants [Ox], non–mineral dust particles, and pollen) if each had an increased OR for asthma hospitalization with various cut-off values and various lag structures up to lag 0 to 6 (Days 0–6). Then these other air pollutants were each examined by a two-compartment model approach to determine if they had an effect on the OR of heavy dust event to asthma hospitalization. Finally, we conducted a conditional logistic regression to obtain the best fit OR using heavy dust event, the climatic variables described above, and other air pollutants described above as independent variables.

The same conditional logistic regression analysis was conducted on each subgroup of sex and age defined *a priori* (ages 1–5 yr, 6–12 yr, 13–15 yr).

We also conducted the same conditional logistic regression using a heavy dust event defined by a more conventional method, suspended particulate matter (daily average particulate matter level ≥ 0.1 mg/m^3), as an exposure measurement. R version 2.9.2 was used for statistical analysis. Additional detail on the method for making these measurements is provided in an online data supplement.

RESULTS

Subjects

During the study period, there were a total of 620 initial hospitalizations for asthma in children who were 1 to 15 years of age. The hospitalization characteristics are described in Table 1. There were more male than female pediatric asthma admissions, consistent with previously published global and regional reports (37). Half of the admissions were for children aged 2 to 5 years. Admissions were most frequent in the month of April and in 2006.

Mineral Dust Levels and Other Air Pollutant Levels

Daily average mineral dust levels greater than 0.1 mg/m^3 were recorded on 6 days in Toyama during the study period (Figure 1). Other air pollutant levels and meteorological observations during the study period are shown in Table 2. Correlations between mineral dust levels and air pollutants or meteorological variables are presented in Table E1 in the online supplement. There were no particularly strong correlations among them. In the local area during the study period, cedar was the major source of pollen, and cypress pollen was also observed in a lesser amount.

Relationship between Heavy Mineral Dust Exposure and Asthma Hospitalization

Figure 2 shows the crude ORs for the relationship between asthma hospitalizations and a heavy dust event on the day of the admission (lag 0) and on the previous cumulative 1 to 7 days (lag 0–1 to lag 0–7). A statistically significant association was shown between asthma hospitalization and a heavy dust event. The crude OR of the heavy dust event for hospitalization on the day was 1.88 (95% CI, 1.04–3.41; $P = 0.037$). The positive association was maintained regardless of the hazard period studied. The crude OR of heavy dust event on any day during the previous week (lag 0–6) was 1.83 (95% CI, 1.31–2.56; $P = 0.00043$).

A crude association between climatic observations and asthma hospitalization is shown in Table E2. Asthma hospitalization had apparent associations ($P < 0.1$) with average temperature, air pressure difference from the previous day, and humidity. We conducted a conditional logistic regression with hospitalization as the dependent variable and as independent variables, heavy dust event and climatic variables with apparent association for asthma hospitalization described above, and we obtained the climatically adjusted OR of 1.86 (95% CI, 1.32–2.62; $P = 0.00037$) for heavy dust event during the previous week.

Table 3 shows the OR and climatically adjusted OR for the heavy dust event (lag 0–6) taking into consideration one of the

TABLE 1. DEMOGRAPHICS OF HOSPITALIZATIONS

	No. (%)		
Sex			
Male	367 (59)		
Female	253 (41)		
Total	620 (100)		
Age, yr	Male	Female	All
1	133	52	185 (30)
2–5	178	132	310 (50)
6–12	52	65	117 (19)
13–15	4	4	8 (1)
Total	367	253	620 (100)
Mean	3.2	4.2	3.6
Median	2	3	2

	No. (%)
Month	
Feb	175 (28)
Mar	199 (32)
Apr	246 (40)
Total	620 (100)
Year	
2005	151 (24)
2006	170 (27)
2007	90 (14)
2008	118 (19)
2009	91 (15)
Total	620 (100)

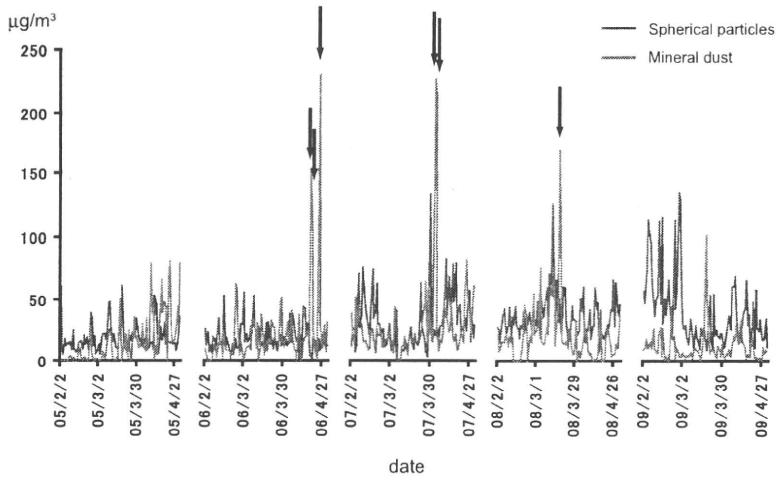

Figure 1. Daily levels of mineral dust particles (nonspherical particles) and nonmineral dust particles (spherical particles) during the study period. *Red* represents mineral dust level, and *blue* represents nonmineral dust level. *Arrows* represent the days with more than 0.1 mg/m³ mineral dust particle levels.

other pollutants (two-pollutant model). For each two-pollutant model, we examined various models with various lag structures from 0 to 0 to 6 days, and various cut-off levels, but the single-pollutant effect of heavy dust event was only slightly attenuated by other pollutants and remained significant after adjustment in all models. Table 3 shows the OR of heavy dust events for asthma hospitalization in the two-pollutant model using results from a model that showed the strongest association with asthma hospitalization for each other pollutant. The final model for obtaining the adjusted OR of heavy dust event for asthma hospitalization was determined to be the one with the climatic variables and other pollutant variables described above. The best fit OR of heavy dust event for asthma hospitalization was 1.71 (95% CI, 1.18–2.48; $P = 0.0050$).

We also conducted the same conditional logistic regression using a heavy dust event defined by suspended particulate matter as an exposure measurement, and a statistically significantly increased OR was shown using this method (Figure E4).

Figure 3 presents the crude OR of heavy dust event for asthma hospitalizations in each sex group and subgroup defined *a priori* (ages 1–5 yr, 6–12 yr, and 13–15 yr). The associations were particularly strong for boys. The risk for hospitalization on the day of heavy dust event was particularly high for boys (OR, 2.32; 95% CI, 1.10–4.87) and for elementary school ages (OR, 3.33; 95% CI, 1.02–10.92), whereas the risk for hospitalizations the following week seemed similar among the subgroups.

DISCUSSION

In this study, heavy mineral dust exposure was significantly associated with an increased risk of asthma hospitalization in children. Although we presumed in the study protocol that a high association would be observed during 3 days after mineral dust exposure, a high association was maintained even after 4 to 6 days after the exposure. This is, as far as we know, the first report that showed a clear association between mineral dust exposure and increased risk of asthma hospitalization. Previously reported efforts to investigate the association between desert dust exposure and asthma exacerbation included two studies in the Caribbean islands on Sahara dust, one in Australia on local dust, and one in Taiwan and three in Korea on Asian dust (15–20). All but the Korean studies showed subtle linkage, or did not show obvious associations with visits or admissions for asthma. The studies from Korea showed a significant decrease in peak flow for children and adults with asthma on Asian dust days, although a quantitative definition of Asian dust days was not presented in the reports, and effects of other air pollutants were not taken into consideration (17, 19, 20). In all these studies, there were some days that had particulate matter greater than 0.1 mg/m³ during the study periods. Possible explanations for the variety of results would be difference in exposure measurement, study design, and the general knowledge of people about the risk of dust, and local variation of size, chemical, mineralogical, and microbiological composition of dust particles.

TABLE 2. FREQUENCY DISTRIBUTION OF THE DAILY LEVELS FOR AIR POLLUTANTS AND METEOROLOGICAL OBSERVATIONS DURING THE STUDY PERIOD

	Days	Mean	SD	25th percentile	Med	75th percentile
Mineral dust particles, μg/m³	400	21.27	25.66	7.82	15	25.08
Non-mineral dust particles, μg/m³	446	28.05	20.55	4.6	22.87	35.77
Suspended particulate matter, μg/m³	446	17.52	11.68	9	14	23
NO_2, ppm	446	12.61	5.85	8	12	17
SO_2, ppm	446	0.86	0.69	0	1	1
Ox, ppm	446	35.17	9.79	29	36	41
Pollen, /cm²	400	31.8	76.7	0	3	21
Average temperature, °C	446	7.64	4.86	3.8	7.2	11.2
Temperature difference from the previous day, °C	446	0.15	2.9	−1.4	0.3	1.8
Temperature difference within the day, °C	446	9.1	3.7	6.2	8.8	1.2
Average air pressure, hPa	446	1,014.7	6.34	1,010.1	1,015.2	1,019.5
Air pressure difference from the previous day, hPa	446	−0.01	0.29	−3.90	0.55	4.20
Wind speed, m/s	446	6.7	2.6	4.6	6.2	8.4
Humidity, %	446	74.4	12.4	66	76	84

Definition of abbreviations: Ox = photochemical oxidants.

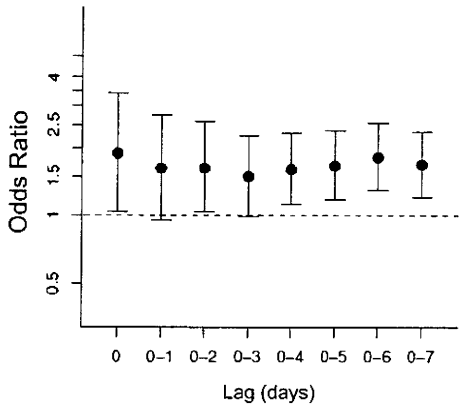

Figure 2. Crude odds ratios for the relationship between asthma hospitalizations and heavy mineral dust exposure (daily average level > 0.1 mg/m^3) on the day of the admission (lag 0) or the previous 1 to 7 days (lag 0–1 to lag 0–7). Error bars represent 95% confidence intervals.

The size distribution of Asian dust particles being lifted into the air and carried to Japan had a peak of 4 μm, and ranged mostly from 0.5 to 10 μm in diameter. Particles this size can penetrate into the lower respiratory system and particles less than 2.5 μm in diameter can enter the gas-exchange region of the lung (2).

Asian dust contains silica and alumina as the main component (6). Quartz, an amorphous and crystalline silica, and aluminum have been reported to cause inflammatory responses with the release of inflammatory cytokines in the lungs of rats (7, 8, 38). Furthermore, Asian dust contains various chemical compounds, including sulfate (SO_4^{2-}) or nitrate (NO_3^-), derived from alkaline soil, which capture acidic gases, such as sulfur oxides (SO_2) and nitrogen oxides (NO_2), during its transportation (39). Hiyoshi and colleagues reported that Asian dust and ovalbumin administered into mice demonstrated an enhanced adjuvant effect of sand dust on ovalbumin-specific IgG1 production when administered together with sulfate (40).

Another important constituent is organics, such as bacteria, fungi, viruses, and other microorganisms. During Asian dust events in Taejon, Korea, the bacterial cfu concentration increased on average 4.3 times over that observed under normal atmospheric conditions (41). Griffin reported that Asian dust included the known allergenic fungi (2). Dust-borne microorganisms in particular can directly impact the immune system of individuals sensitive to those agents, and lipopolysaccharide or β-glucan included in the microorganisms are known pattern-associated molecular patterns that activate dendritic cells to mount an immune response (42). A study by Ichinose and colleagues demonstrated that inhalation of dust sand from Tengger Desert (China), which had higher amounts of β-glucan than dust from the Maowusu Desert (Inner Mongolia), caused greater eosinophil infiltration in the murine airway than did dust from the Maowusu Desert (43). Another study further showed that the heated desert sand, in which microbiological materials and sulfate were excluded by heating, had less effect on allergic lung inflammation (44). Accordingly, quartz, sulfate, and microbiological materials would be included in the pathogenicity of desert sand.

The measured quartz content in a major dust storm is very similar between Asian dust and African dust (60.95% in North Africa and 60.26% in China), and the concentrations of culturable bacteria and fungi and fungal spores in dust storms are greatly elevated relative to background in most investigated places (2, 45). Accordingly, it is quite possible that not only in East Asia but also in many other areas where windborne desert dust is observed, desert dust exposure greatly contributes to asthma admissions of children.

In our study, there were no heavy dust event days in 2005, yet 25% of the hospitalizations occurred in that year. There was a downward trend in hospitalizations from 2007 to 2009 compared with 2006, yet there were three heavy dust event days during this period. Although the desert dust exposure was shown as an independent risk for asthma hospitalization in this study, the contribution of heavy dust events to the total number of asthma hospitalization may be limited in Japan. This is reasonable considering that the heavy dust event occurred only on 6 days of the 446 days of the study period. The heavy dust events may be a more substantial contributor to the total number of asthma hospitalizations in some other parts of the world where dust events occur more frequently than in Japan.

Not only desert dust but also infections, irritants such as tobacco smoke, and other pollutants are also known to exacerbate asthma. In our study, other than heavy dust events, we found statistically significant associations with asthma hospitalization in gaseous NO_2, gaseous SO_2, gaseous Ox, nonmineral particles, and pollen in some cut-off levels in some lag periods. Similarly, we observed an increased OR when using particulate matter count for an exposure measurement, although this method does not clearly differentiate mineral dust from other particles. Thus, using LIDAR system, it would be possible to caution children with asthma to avoid exposure to heavy dust environments.

In the present study, the risk of mineral dust for asthma hospitalization was particularly high for boys (Figure 3A). Especially, the risk on the first day of the exposure was high for boys and for elementary school ages (6–12 yr old), whereas girls and infants (1–5 yr old) showed the increased risk later in the week (Figure 3B). The percentage of elementary school ages among all ages in boys (14%) was lower than in girls (26%). Accordingly the stronger association observed in boys

TABLE 3. ODDS RATIO OF HEAVY DUST EVENTS FOR ASTHMA HOSPITALIZATION ADJUSTED BY OTHER POLLUTANTS IN TWO-POLLUTANT MODEL

		Two-pollutant Model Adjusted by				
	Single-Pollutant Model	Non-M Dust	Pollen	NO_2	SO_2	Ox
Crude OR	1.83	1.79	2.04	1.70	1.80	1.63
95% CI	1.31–2.56	1.28–2.51	1.44–2.88	1.21–2.39	1.28–2.55	1.15–2.29
Climatically adjusted OR	1.86	1.83	2.19	1.76	1.86	1.66
95% CI	1.32–2.62	1.30–2.58	1.50–3.04	1.25–2.48	1.31–2.64	1.17–2.35

Definition of abbreviations: CI = confidence interval; Non-M dust = non-mineral dust particles; OR = odds ratio.

Non-mineral dust (on the day: lag 0 d) and pollen (on the previous day: lag 1 d) was treated as a five-level variable, NO_2 was treated as dichotomous (with cut-off value of 80th percentile and cumulative lag 0–5 d), and SO_2 (on the day: lag 0 d) was treated as a five-level nominal variable.

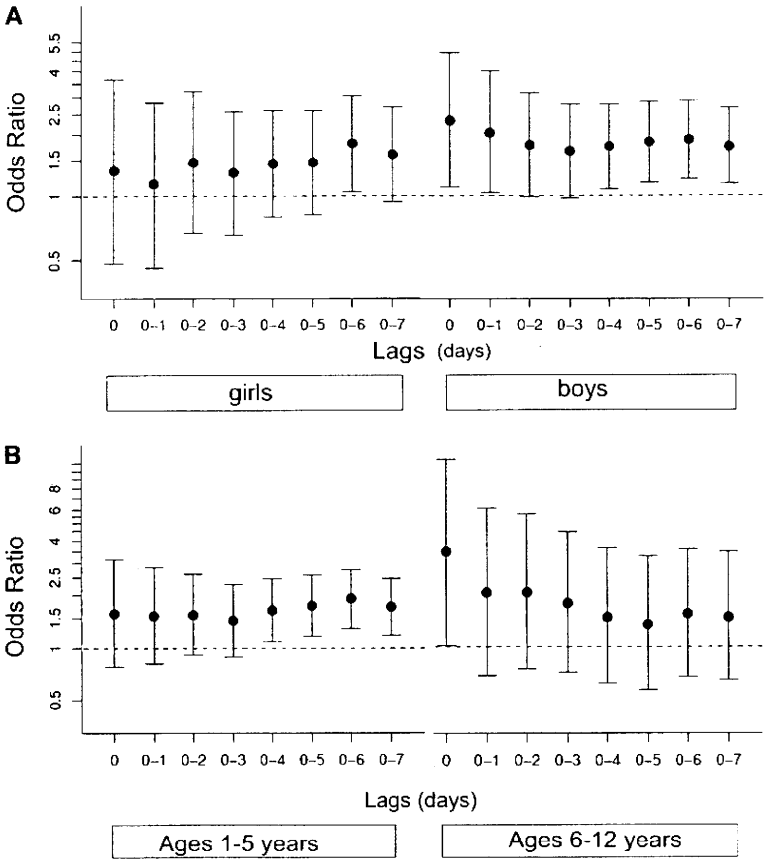

Figure 3. Crude odds ratios of heavy mineral dust exposure (daily average level > 0.1 mg/m^3) for asthma hospitalizations on the day of the admission (lag 0) or the previous 1 to 7 days (lag 0–1 to lag 0–7) in each subgroup. (*A*) Girls (n = 253) and boys (n = 367). (*B*) Children aged 1 to 5 years (n = 495) and 6 to12 years (n = 117). Error bars represent 95% confidence intervals.

cannot be explained by the distribution of ages. It is interesting that boys showed a higher OR in heavy dust events and girls showed a higher OR for other air pollutants, such as NO_2, SO_2, and Ox, in our study. The high risk on the first day observed in boys and in elementary school–aged children may have been influenced by any of several factors: length of exposure to outdoor air, exercise in outdoor air, or any immune mechanism that might make these groups more susceptible to mineral dust particles. Further investigations should be conducted to investigate if there are any differences in pathogenesis between the earlier asthma symptoms and later ones and to determine if there are especially susceptible subpopulations among patients with asthma, including adults.

Aerosolized particles have various effects on the atmospheric environment, including chemical and radiative effects, and also on the oceanic environment (2). It is not realistic to eliminate the dust events, which would negatively influence living creatures in various ways. However, we believe that we can at least minimize the detrimental effects of desert dust exposure by giving information to relevant people, so that susceptible children can protect themselves.

Our study has following limitations. First, the interpretation was limited by the occurrence of only six heavy dust event days in the study period. Second, the exposure data were not individually based but were based on measurements in the locality. Accordingly, it is possible that we underestimated the association because of miscategorizations. Third, because we chose hospitalizations for the outcome measure, the study results are generalized only to children who can be hospitalized. However, an observational study in Japan shows that 17.5% of pediatric patients with intermittent mild asthma also experience hospitalization, and accordingly our study result will probably be applicable not only for patients with moderate to severe disease but also for patients with mild disease (46). Last, the associations we found were only for acute effects. Chronic effects should be further investigated.

As for the strength of our study, we used objective measures for both exposure and outcome, so that recall bias or presentation bias could be excluded. Additionally, we used the LIDAR nonspherical extinction coefficient for an exposure measure, so that we could focus on the effect of mineral dust particles.

In conclusion, this study suggested that heavy dust events were significantly associated with the increased risk of asthma admission for children with asthma. Physicians, patients, and the general public, including schools and preschools, should be adequately informed of the health implications of heavy desert dust exposure so that those at risk can minimize the deleterious effects.

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乳幼児喘息の疫学調査のための質問票の妥当性に関する検討

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Key words：乳幼児喘息，疫学調査，質問票

略語：ISAAC：International Study of Asthma and Allergies in Children,
JPGL：Japanese Pediatric Guideline

和文抄録

6歳以上の喘息児に関する疫学調査は，世界共通の質問票（ISAAC）を用いて広く行われているが，乳幼児を対象とした質問票の妥当性に関するエビデンスは少ない．そこで，新たに本邦ガイドライン（JPGL）に準じて作成した質問票の妥当性を検討した．7つの医療施設を受診した5歳以下の児の保護者に『ISAAC基準の質問票』ならびに『JPGL基準の質問票』への回答を依頼し，その回答と医師の判断を0～2歳児と3～5歳児でそれぞれ比較検討した．リクルートされた369名中353例（95.7%）を解析した結果，期間有症率について，0～2歳児では『JPGL基準の質問票』の陽性的中率は0.70であったのに対し，『ISAAC基準の質問票』では0.50と低値であった．一方，3～5歳では，それぞれ0.68と0.74であった．以上より，乳幼児の疫学調査には，2歳以下では『JPGL基準の質問票』を，3歳以上では『ISAAC基準の質問票』あるいは『JPGL基準の質問票』を用いることが適当であると考えられた．

はじめに

気管支喘息に罹患する子どもたちの数は世界的に増加傾向にあり，我が国でもこの20年間で2.1倍に増加している[1)]．その原因を探り治療や予防法を確立するために大規模な疫学調査が必要であり，既にInternational Study of Asthma and Allergies in Children（ISAAC）という世界共通の質問票を用いて調査が行われ，多くの成果が得られている[2-4)]．我々も平成17年に全国の小中学生各々約5万人を対象とした大規模調査を行い，喘息の有症率がそれぞれ13.9%と8.8%であることを，また運動誘発喘息が子どもの生活の質（QOL）を低下させていることを明らかにした[5-6)]．しかし，このISAACの質問票は6歳以上の子どもたち用に開発されたものであり，それ以下の子どもたちでの妥当性に関する十分なエビデンスは得られていない．

ISAACの質問票は，保護者に「胸がゼイゼイまたはヒューヒューするか」と問うもので，喘鳴の有無が重要なポイントとなる．しかし，乳幼児期ではその解剖学的・生理学的特徴から比較的容易に喘鳴を来すことが多く，喘鳴があるからというだけで喘息と診断することはできない．そのため，我が国の小児気管支喘息治療・管理ガイドライン（JPGL）

では，「明らかな呼気性喘鳴を３エピソード以上繰り返した場合に乳児（２歳未満）喘息と診断する」とされており，さらに「エピソードとエピソードの間に無症状な期間が１週間程度以上あること」や「呼気性喘鳴は医師の診察によって判断されることが望ましい」との追加条件も記されている[7]．そこで，本邦での乳幼児における喘息の疫学調査をより正確に行うために，我々はISAACならびにJPGLに準ずる形で保護者向けの質問票を作成し，アレルギー専門医の診断を基準として，その妥当性を検討した．

対象と方法

日本小児アレルギー学会に所属する小児科医７名が所属する医療施設（富山大学附属病院，いからし小児科アレルギークリニック，おのうえこどもクリニック，高重記念クリニック，富山赤十字病院，済生会高岡病院，氷見市民病院）を2007年11月～12月に来院した５歳以下の児の保護者を対象として，ISAACとJPGLに準ずる形で作成した質問票(表１)への回答を依頼した．対象となった児は，必ずしも喘鳴を含めた呼吸器症状を主訴として来院したものではなく，単にそれぞれの医療機関をかかりつけ医としているか，あるいは何らかの疾患のために定期通院しているもののうち，それぞれの医師が過去の経過を理解していると判断されたものとした．なお，重篤な基礎疾患を有する者はリクルートの段階で除外した．表１に示すように，保護者用の質問は4問よりなり，まずＱ１で喘鳴の既往の有無を確認し，「はい」と答えた場合には，Ｑ２からＱ４まで回答してもらった．そして，『ISAAC基準の質問票』での生涯有症率はＱ１で，期間有症率はＱ１＋Ｑ４で「はい」と回答した者で，『JPGL基準の質問票』での生涯有症率はＱ１＋Ｑ２＋Ｑ３で，期間有症率はＱ１＋Ｑ２＋Ｑ３＋Ｑ４で「はい」と回答した者で判定した．一方，医師には，保護者の回答を見ない状態で，それぞれの患児の今までの経過から喘息と診断しているかどうかを，さらに喘息と診断している場合には過去12ヶ月間に喘息症状があったかどうかを文書で確認した．

保護者の回答と医師の判断の一致性を確認するために，カッパ係数を用いて解析し，カッパ係数が＞0.41を比較的良好な相関，＞0.61を良好な相関，＞0.81を極めて良好な相関と判定した[8]．また，質問票の結果と医師の評価との関係について，感度，特異度，陽性的中率，陰性的中率についても検討した．さらに，上記の検討を低年齢児（０～２歳）と高年齢児（３～５歳）に分けても行った．

表１　保護者向け質問票における質問項目と生涯ならびに期間有症率の判定基準

Ｑ１．あなたのお子さまは，今までいずれかの時期に，胸がゼイゼイまたはヒューヒューしたことがありますか　　（はい，いいえ）

Ｑ２．そのようなゼイゼイ，ヒューヒューは１週間以上の間隔をあけて，今までに３回以上ありましたか　　（はい，いいえ）

Ｑ３．そのようなゼイゼイ，ヒューヒューは少なくとも１回以上医師に確認されましたか　　（はい，いいえ）

Ｑ４．あなたのお子さまは，最近12ヶ月のあいだに，胸がゼイゼイまたはヒューヒューしたことがありますか　　（はい，いいえ）

調査目的	質問項目	
	ISAAC基準	JPGL基準
生涯有症率	Q1	Ｑ１＋Ｑ２＋Ｑ３
期間有症率	Ｑ１＋Ｑ４	Ｑ１＋Ｑ２＋Ｑ３＋Ｑ４

表2　対象

年齢（歳）	人数	保護者 今までにゼイゼイ・ヒューヒューしたことあり	医師 喘息と診断されている （既往を含む）
0	23	7 (30.4%)	2 (8.7%)
1	64	39 (60.9%)	23 (35.9%)
2	68	42 (61.8%)	21 (30.9%)
3	65	41 (63.1%)	29 (44.6%)
4	73	63 (86.3%)	47 (64.4%)
5	60	40 (66.7%)	37 (61.7%)
合計	353	232 (65.7%)	159 (45.0%)

結　果

7つの医療施設において369名がリクルートされ，記載不備の16例を除く353例（95.7%）を解析対象とした（表2）．年齢分布は，0歳児を除く各年齢において60～70例ずつで，そのうち今までに喘鳴を認めたことがあると保護者が回答した児の割合は平均で65.7%，また医師が既往も含めて喘息と診断している児は平均で45.0%であった．医師が喘息と診断している児の割合は年齢が増すにつれて高くなっていたが，「今までにゼイゼイ・ヒューヒューしたことがある」と保護者が回答した者の割合は1歳以降では概ね60%以上であった．

保護者用の質問の組み合わせと医師の判断との一致性を検討した結果，生涯有症率調査用の質問（以下，生涯有症率用質問）ではどの組み合わせにおいてもカッパ値が0.6前後と良好に相関し，組み合わせによる大きな差異は認められなかった（表3）．

表3　保護者向け調査票の回答と医師の判断の一致性の検討

A）喘息の生涯有症率調査用質問

保護者への質問	医師による判断（既往を含めた喘息） あり（n=159）	 なし（n=194）	 カッパ値
Q1（喘鳴の既往）	158 (99.4)	74 (38.1)	0.59
Q1＋Q2（エピソード3回以上）	117 (73.6)	29 (14.9)	0.59
Q1＋Q3（医師による喘鳴の確認）	156 (98.1)	65 (33.5)	0.62
Q1＋Q2＋Q3	117 (73.6)	24 (12.4)	0.62

B）喘息の期間有症率調査用質問

保護者への質問	医師による判断（過去12ヶ月間の喘息症状） あり（n=133）	 なし（n=220）	 カッパ値
Q1（喘鳴の既往）＋Q4（過去12ヶ月の症状あり）	118 (88.7)	77 (35.0)	0.49
Q1＋Q2（エピソード3回以上）＋Q4	91 (68.4)	39 (17.7)	0.50
Q1＋Q3（医師による喘鳴の確認）＋Q4	117 (88.0)	70 (31.8)	0.52
Q1＋Q2＋Q3＋Q4	91 (68.4)	35 (15.9)	0.53

また，期間有症率調査用の質問（以下，期間有症率用質問）でもカッパ値が0.5前後と比較的良好な相関が認められ，質問の組み合わせによる差異は小さいものであった．一方，ISAACならびにJPGL基準と医師の判断との関係を検討したところ，全対象では，生涯有症率用質問の感度／特異度はそれぞれ0.99／0.62 と0.74／0.88であり，陽性的中率もそれぞれ0.68ならびに0.83であった（表4）．また，期間有症率用質問においても，生涯有症率用質問と同程度の感度／特異度，陽性的中率を認めていた．

さらに，これらの対象を低年齢児（0～2歳，n=155）と高年齢（3～5歳，n=198）に分けて同様の検討を行ったところ，2歳以下の児においてはISAAC基準では，生涯有症率用ならびに期間有症率用質問の陰性的中率は0.95以上と高率であったが，陽性的中率はそれぞれ0.52と0.50と低率であった（表4）．一方，3～5歳児では，ISAAC基準の期間有症率用質問の陽性的中率が0.68であった以外は，いずれも陽性ならびに陰性的中率は7割を超えていた．

表4　年齢による妥当性の違い

A) 生涯有症率調査用質問

	カッパ値	感度	特異度	陽性的中率	陰性的中率
全対象					
ISAAC基準	0.59	0.99	0.62	0.68	0.99
JPGL基準	0.62	0.74	0.88	0.83	0.80
0－2歳					
ISAAC基準	0.49	1.00	0.61	0.52	1.00
JPGL基準	0.59	0.72	0.87	0.70	0.88
3－5歳					
ISAAC基準	0.64	0.99	0.62	0.78	0.98
JPGL基準	0.61	0.74	0.88	0.89	0.72

B) 期間有症率調査用質問

	カッパ値	感度	特異度	陽性的中率	陰性的中率
全対象					
ISAAC基準	0.49	0.89	0.65	0.61	0.91
JPGL基準	0.53	0.68	0.84	0.72	0.81
0－2歳					
ISAAC基準	0.44	0.91	0.64	0.50	0.95
JPGL基準	0.59	0.73	0.87	0.70	0.89
3－5歳					
ISAAC基準	0.52	0.88	0.66	0.68	0.87
JPGL基準	0.48	0.66	0.81	0.74	0.75

考　案

ISAACならびにJPGLに準じて作成された保護者用質問票を5歳以下の小児における喘息の有無を判断する妥当性を検討した結果，両者共に医師の判断と概ね良好な相関が得られることが明らかとなった．しかし，対象となった乳幼児を0～2歳と3～5歳の2群に分けて同様の検討を行ったところ，0～2歳児に『JPGL基準の質問票』の陽性的中率は約7割と高率であったが，『ISAAC基準の質問票』では50%程度と低率であった．一方，3～5歳児では，いずれの質問票でも陽性ならびに陰性的中率は約7割を超えていた．

低年齢児では呼吸器における解剖学的・生理的特徴によって喘息以外の病態でも喘鳴を呈することが多い反面，保護者には喘鳴であるかどうかの判断が難しい場合もあり，喘鳴の有無が主たる質問となる『ISAAC基準の質問票』では喘息かどうかの判定は難しいと考えられる．Hederosらは，6歳以下の子どもたちの保護者を対象としてISAACに基づく質問票の結果と医師による喘息との診断とを比較したところ，全体としては感度が77%，特異度が97.5%と良好な結果であったが，年齢別に解析すると，2歳以下では感度が22%と低値であることを報告している[9]．また，Dela Biancaらは独自に作成した質問票の妥当性を170名の1～3歳の児を対象として検討し，医師の診断とよく一致したと報告している[10]．しかし，その質問内容は，喘息治療薬の使用の有無や入院エピソードの有無，喘息の家族歴，本人の食物アレルギーの合併の有無など多岐にわたり，オリジナル版では45問，縮小版でも18問と質問数が多く，大規模な疫学調査には不向きと思われる．また，Øienらが2-6歳向けに開発した質問票には喘鳴の有無を問う項目は含まれておらず，「医師によって喘息と診断されことがあるか」や「喘息として治療をうけたり入院したことがあるか」という項目で構成されている[11]．

我々が作成した『JPGL基準の質問票』は，喘鳴の有無以外に，喘鳴エピソードが3回以上かどうか，エピソードの間隔は1週間以上空いているかどうか，さらに喘鳴は医師によって確認されているかどうかの質問項目からなる．その結果，0～2歳の低年齢群においても『ISAAC基準の質問票』よりも高い陽性的中率が得られたことより，低年齢児の調査には『ISAAC基準の質問票』よりも『JPGL基準の質問票』の方が適していると思われる．また，島らが環境省の『そらプロジェクト』のために新たに開発した質問票では，まず「息をするときのヒューヒュー・ゼーゼーなどの音」に関する質問で喘鳴を呈する児を抽出し，その上で喘鳴エピソードの回数や呼吸困難を伴っていた回数なども質問している．その妥当性の検討は，5つの医療機関を受診した喘息またはその他の呼吸器・アレルギー症状のある1歳台の小児65例を対象とし，喘息の有無はその時の診察医の判断によってなされ，それぞれの質問項目の感度・特異度などで評価している[12]．その結果，喘息以外の児においても約半数に喘鳴の既往があるために，喘鳴のエピソードに加えて「2回以上の呼吸困難あり」の児を喘息と判断するのが妥当と結論づけている．我々の作成した質問項目には「呼吸困難」が含まれていないが，保護者によって呼吸困難の定義が異なる可能性もあり，さらなる検討が必要であろう．一方，3歳以上の児については，今回の検討では『ISAAC基準の質問票』と『JPGL基準の質問票』の間に大きな差異は認められなかった．前述したHederosらの報告にもあるように[9]，この年齢層以上では世界共通の質問票であるISAACの質問票で対応可能と思われる．そして，実際に4～5歳児1500名以上を対象とした疫学調査にも既に用いられている[13]．

一方，我々の検討には問題点もある．今回の対象は，医療機関を受診した患者であり，またそのうち喘鳴を認める頻度も通常の一般人口に比して高値であることからも対象に偏りがあると思われる．この偏りが今回の結果に影響した可能性は否定できず，今後，一般の子どもたちを対象として検討すべきであろう．しかし，このような質問票の妥当性を検証する際には喘息の有無を判断する客観的指標が必要であるが，現時点では医師の判断によるところが大きい．しかし，医師間のバラツキも否定できないために，今後乳幼児においても呼吸機能や呼気一酸化窒素など客観的指標を導入していくことが必要であろう．さらに，現段階では乳幼児喘息の診断については世界的なコンセンサスは得られていないために[14]，今回の検討の根拠としたJPGLの基準が世界的に妥当であるかは明らかではない．しかし，本邦で診療を行ううえでは，本邦のガイドラインに則して診断・治療することが適当と考えられ，今回の結

果は少なくとも我が国の実状調査を行う上での参考になると考える.

以上より，乳幼児喘息の疫学調査を行う際には，2歳以下の児に対しては『JPGL基準の質問票』を，3歳以上の児に対しては『ISAAC基準の質問票』あるいは『JPGL基準の質問票』を用いることが適当であると思われた．より正確な疫学調査を行うことによって，今後乳幼児喘息の治療や予防法確立に必要なデータの蓄積が行われることが期待される.

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気管支喘息

診療ガイドラインの解説

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2．気管支喘息

1）診療ガイドラインの解説

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KEY WORDS　気管支喘息，ガイドライン，早期介入，コントロールレベル

はじめに

喘息に関するガイドラインは，1991年に米国でNIHが国内向けにExpert Panel Report（EPR）を，1995年にWHOが世界に向けたGINA（Global Initiative for Asthma）を，さらに本邦では1998年に日本アレルギー学会が喘息予防・管理ガイドラインを発表した。小児に関しては，2000年に日本小児アレルギー学会が小児に特化した小児気管支喘息治療・管理ガイドライン（JPGL）を発表し，その後新たなエビデンスを加えながら改訂を重ねて現在に至っている（図1）。この約20年間，ガイドラインの普及によって喘息の診療形態は大きく様変わりした。喘息死や長期施設入院療法を必要とする例が激減し，さらに一般病院でも発作入院の数が減少傾向にある。このようにガイドラインは一定の効果を示してきたが，最近行われた電話調査では，喘息児のうち過去1カ月間に日中や夜間に喘息症状を認めた児の割合はそれぞれ50%，33%と高く，さらに過去1年間に発作のために学校や幼稚園などを欠席した児の割合は49%に及んでおり[1]，現在のガイドラインはさらに進化を遂げる必要があると思われる。本稿では，本邦のガイドラインの特徴，ガイドラインにおける問題点や今後の課題について，諸外国のガイドライン（EPRとGINA）と比較して概説する。

Ⅰ．JPGLの特徴

1．より早期からの介入

最大の特徴は，EPRやGINAに比して早期からの長期管理を推奨していることである（**表-A**）。これは，わが国では国民皆保険制度があるために，他国に比してより早期から十分な医療を提供できることが一因と考えられる。一方，吸入ステロイド薬（ICS）を用いてより早期から介入を行っても喘息の自然歴を変えることはできなかったという結果が複数の大規模研究から出されている[2)3)]。この結果を「より早期からの介入には臨床的意義が無い」と解釈することもできるが，ICSによる治療中はプラセボに比して有意に喘息

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