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Does Environment Mediate Earlier Onset of the Persistent Childhood Asthma Phenotype?

Ramesh J. Kurukulaaratchy, MRCP; Sharon Matthews, RGN; and S. Hasan Arshad, DM, FRCP

ABSTRACT. *Objective.* We investigated the role of environmental and hereditary factors in determining whether persistent childhood wheezing phenotypes had an early or late onset.

Methods. In a whole population birth cohort ($n = 1456$), children were seen at birth and at 1, 2, 4, and 10 years. At each visit, information was collected prospectively regarding wheeze prevalence and used to classify subjects into wheezing phenotypes. Information on genetic and environmental risk factors in early life was also obtained prospectively, and skin-prick testing to common allergens was performed at 4 years.

Results. Early-onset persistent wheezers ($n = 125$) had wheeze onset in the first 4 years, still present at age 10, whereas late-onset persistent wheezers ($n = 81$) had wheeze onset after age 4 years that was still present at 10 years. Multivariate logistic regression analysis identified independent significance only for inherited factors (parental asthma, family history of rhinitis, eczema at 4 years, and atopic status at 4 years) in the development of late-onset persistent wheeze. However, low social class at birth, recurrent chest infections at 2 years, and parental smoking at 2 years plus inherited factors (eczema at 2 years; food allergy at 4 years; maternal asthma, sibling asthma, maternal urticaria, and atopic status at 4 years) demonstrated independent significance for early-onset persistent wheeze.

Conclusion. Inheritance seems to be of prime significance in the cause of persistent childhood wheeze. Environmental exposure in early life may combine with this tendency to produce an early onset of persistent wheeze. Absence of these environmental factors might delay but not prevent the onset of wheeze in children with atopic heredity. *Pediatrics* 2004;113:345–350; *childhood asthma, environment, heredity, persistent wheeze, risk factors.*

ABBREVIATION. IgE, immunoglobulin E.

It is recognized that rather than being a single disorder, childhood wheezing represents a spectrum of distinct phenotypes.¹ This realization has led to an enhanced understanding of the nature of childhood wheezing and the mechanisms that might underlie its development. Whereas some wheezing phenotypes provide an extremely transient disorder not typical of childhood asthma, others more closely

conform to the accepted notion of this disease. Thus, the Tucson Children's Respiratory Study^{2,3} characterized the early-onset persistent wheezer as possessing high levels of atopy, impaired lung function, and bronchial hyperresponsiveness. Accordingly, work from the Childhood Asthma Management Program study⁴ has shown that children with longest duration of wheezing may experience greatest disease severity. It is clear, therefore, that the early-onset persistent wheezer harbors great potential to develop troublesome asthma. A group of late-onset persistent childhood wheezers^{1,3} who closely parallel the characterization of an early-onset persistent wheezer yet remain asymptomatic in early life have also been identified. We have confirmed these similarities in our own British cohort⁵ that has now been followed for the first decade of life. Rather than being 2 distinct states, early- and late-onset persistent wheezing may simply represent differing manifestations of the same largely atopic persistent childhood asthma phenotype. Understanding why some children manifest this phenotype in early childhood whereas others do not do so until later can provide a better understanding of how persistent childhood asthma arises and of what, if anything, can be done to prevent its development. Results from the Tucson study² suggest that in their population, eczema, maternal smoking, and Hispanic ethnicity were associated with earlier manifestation of persistent wheeze. Here we describe findings from our British unselected whole population birth cohort that provide additional insight into this issue.

METHODS

A whole population birth cohort was established on the Isle of Wight, UK, in 1989 to study prospectively the natural history of childhood asthma and to identify risk factors relevant to its development. Approval for the study was obtained from the Local Research Ethics Committee. Of 1536 children who were born between January 1, 1989 and February 28, 1990, informed consent was obtained to enroll 1456 subjects. Enrollment took place at birth, and information on allergic family history (parental or sibling), household pets, smoking habit, social class, and birth weight were recorded. Cord blood immunoglobulin E (IgE) was measured in most instances at birth. Children were followed at the ages of 1 ($n = 1167$; 80.2%), 2 ($n = 1174$; 80.6%), 4 ($n = 1218$; 83.7%), and 10 years ($n = 1373$; 94.3%). Results of cohort follow-up (1, 2, 4, and 10 years) have been reported previously.^{6–9} At every follow-up, detailed questionnaires were completed with the parents for each child regarding asthma and allergy prevalence. "Current wheeze" was recorded as occurring in the previous 12 months. Exposure to relevant environmental factors (domestic pets and tobacco smoke) was noted. Method of feeding was obtained at 1 and 2 years. A history of recurrent chest infections (>1) was assessed at 1 and 2 years of age. Investigators' diagnoses of

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eczema (chronic or chronically relapsing itchy dermatitis lasting >6 weeks with characteristic morphology and distribution), recurrent nasal symptoms/rhinitis (recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes), and food allergy (history of vomiting, diarrhea, colic, or rash within 4 hours of ingestion of a particular food on at least 2 occasions) were made at 1, 2, and 4 years. Skin-prick testing was performed in most children seen at 4 years⁸ ($n = 981$) to a panel of common inhaled and food allergens (Biodiagnostics, Reinbek, Germany). This comprised house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, cat and dog epithelia, *Alternaria alternata*, *Cladosporium herbarium*, milk, hen egg, soya, cod, wheat, and peanut plus histamine and physiologic saline to act as positive and negative controls respectively. Mean wheal diameter of at least 3 mm greater than the negative control was regarded as a positive reaction.

Analysis

Data were double entered onto SPSS (v10.0; SPSS Inc, Chicago, IL). Children were categorized at 10 years into phenotypes by presence of "current wheeze" at each follow-up. Nonwheezers never wheezed during the first decade of life, early-onset persistent wheezers had wheezing onset during the first 4 years of life and still wheezed at 10, and late-onset persistent wheezers had wheezing onset after 4 years of age and still wheezed at 10 years. For minimizing recall bias and improving accuracy, analysis in this article is restricted to 1034 (71%) of the original 1456 cohort who were seen prospectively with information at all study visits; 1 or 2 years and 4 and 10 years. These 1034 children did not differ demographically or in major disease parameters from 339 subjects who were observed at 10 years but excluded from the present analysis because of previous missing follow-up.⁵

Separate univariate risk factor analysis was conducted for early-onset and late-onset persistent wheeze to identify factors that were present in early life (the first 4 years) and were capable of predicting risk of developing each of these states. χ^2 analysis (with

Fisher exact test where indicated by low expected cell counts) was used for this purpose comparing factors between each persistent wheezing phenotype and the nonwheezing state. For obtaining the independent effect of risk factors showing trends for significance at univariate testing ($P < .2$), separate logistic regression models were created for development of early-onset persistent wheeze and late-onset persistent wheeze. Stepwise backward (likelihood ratio) logistic regression was used for this purpose. When >1 risk factor could explain a particular exposure of interest, the most relevant only was entered into the model.

RESULTS

By 10 years, the cumulative prevalence of wheeze ever was 40.3% (417 children) among the group of 1034 children with full prospective follow-up. Of these, 125 (30.0%) were early-onset persistent wheezers and 81 (19.4%) were late-onset persistent wheezers. The remainder of wheezing children had transient wheezing of early onset. Characterization of these wheezing phenotypes has been described elsewhere.⁵

Risk Factors for Early-Onset Persistent Wheeze

Factors that showed statistical significance ($P < .05$) at univariate analysis for development of early-onset persistent wheeze are identified in Table 1. Male sex carried an increased risk for this state. Personal histories of diagnosed allergy at 1 year (eczema, rhinitis, and food allergy), 2 years (eczema, rhinitis, and food allergy), and 4 years (eczema, rhinitis, and food allergy) were significant risk factors

TABLE 1. Univariate Risk Analysis for Development of Early-Onset Persistent Wheeze ($P < .05$)

Factor	Prevalence in Wheeze Phenotype		P Value	OR	95% CI
	Early Persistent	Non			
Atopic SPT 4 y	46.8% (52/211)	14.6% (75/515)	<.001	5.17	3.31–8.08
Eczema 1 y	27.2% (34/125)	6.3% (39/617)	<.001	5.54	3.32–9.22
Rhinitis 1 y	14.4% (18/125)	5.2% (32/617)	<.001	3.08	1.67–5.68
Food allergy 1 y	16.8% (21/125)	5.0% (31/617)	<.001	3.82	2.11–6.90
Eczema 2 y	18.4% (21/114)	8.4% (52/617)	.001	2.45	1.41–4.26
Rhinitis 2 y	18.4% (21/114)	5.5% (34/617)	<.001	3.87	2.15–6.96
Food allergy 2 y	8.8% (10/114)	1.9% (12/617)	<.001	4.85	2.04–11.51
Eczema 4 y	23.4% (29/124)	8.9% (55/617)	<.001	3.12	1.89–5.14
Rhinitis 4 y	16.8% (21/125)	2.8% (17/616)	<.001	7.12	3.63–13.94
Food allergy 4 y	8.1% (10/124)	1.6% (10/616)	<.001	5.32	2.16–13.06
Maternal asthma	27.9% (34/122)	13.0% (77/592)	<.001	2.58	1.63–4.10
Sibling asthma	42.6% (52/122)	26.5% (157/592)	<.001	2.06	1.38–3.08
Paternal eczema	12.4% (15/121)	6.9% (41/592)	.042	1.90	1.02–3.56
Parental eczema	31.1% (38/122)	20.1% (119/592)	.007	1.80	1.17–2.77
Maternal urticaria	13.1% (16/122)	6.4% (38/592)	.011	2.20	1.18–4.09
Parental urticaria	14.9% (18/121)	7.9% (47/592)	.016	2.03	1.13–3.63
Parental allergy	70.5% (86/122)	58.1% (344/592)	.011	1.72	1.13–2.63
Male sex	59.2% (74/125)	46.5% (287/617)	.010	1.67	1.13–2.47
Social class I–III at birth	38.7% (29/75)	51.7% (184/356)	.040	0.59	0.35–0.98
Early weaning (first 3 mo)	22.3% (27/121)	14.0% (83/594)	.020	1.77	1.09–2.88
Exclusive breastfeeding first 3 mo	20.0% (24/120)	39.4% (227/576)	<.001	0.38	0.24–0.62
Exclusive formula feeding first mo	49.2% (59/120)	35.7% (214/599)	.006	1.74	1.17–2.58
Parental smoking at birth	52.0% (64/123)	36.6% (223/609)	.001	1.88	1.27–2.77
Parental smoking 1 y	51.2% (64/125)	33.9% (208/614)	<.001	2.05	1.39–3.02
Parental smoking 2 y	51.8% (58/112)	35.0% (212/606)	.001	2.00	1.33–3.00
Parental smoking 4 y	52.8% (66/125)	33.2% (205/617)	<.001	2.25	1.52–3.32
Chest infections 1 y	21.6% (27/125)	1.8% (11/617)	<.001	15.18	7.29–31.59
Chest infections 2 y	42.1% (48/114)	2.8% (17/617)	<.001	25.67	13.96–47.18

OR indicates odds ratio; CI, confidence interval; SPT, skin-prick test. Comparison is between early-onset persistent and nonwheeler. Only factors that showed statistical significance at univariate analysis ($P < .05$) are shown. Additional factors that demonstrated trends for significance ($P > .05$ but $< .2$) were paternal asthma, maternal eczema, sibling urticaria, cat ownership (at birth, 4 years), and dog ownership (at birth, 2 years and 4 years). Factors that did not show trends for significance ($P > .2$) were sibling eczema, paternal urticaria, individual/combined family histories of food allergy; individual/combined family histories of rhinitis, cat ownership (1 and 2 years), and dog ownership (1 year).

for early-onset persistent disease, as was atopic sensitization at 4-year skin-prick testing. Family history of allergic disease, too, showed significant risk for this state, with maternal and sibling asthma, paternal eczema, and maternal urticaria conferring significantly increased univariate risk. Recurrent chest infections at 1 and 2 years were also associated with having early-onset persistent wheeze, as were parental smoking at birth and at 1, 2, and 4 years and early introduction of solids (within the first 3 months of life). Conversely, higher social class at birth (class I–III) was associated with significant risk reduction of early-onset persistent disease, as was exclusive breastfeeding in the first 3 months of life. Statistically nonsignificant trends for reduced risk of early-onset persistent wheeze were noted for cat ownership at birth and 4 years, as well as dog ownership at birth, 2 years, and 4 years. Cord IgE at birth did not differ significantly between early-onset persistent and nonwheezers (median: 0.1 vs 0.1; $P = .818$, Mann-Whitney U test).

Risk Factors for Late-Onset Persistent Wheeze

Factors that demonstrated statistical significance ($P < .05$) at univariate analysis for development of late-onset persistent wheeze are listed in Table 2. Male sex carried a nonsignificant trend for increase risk of late-onset persistent disease, whereas social class at birth held no association. Eczema in early life (1, 2, or 4 years) was a significant risk factor for disease, as was atopic sensitization at 4 years. Both maternal and paternal asthma carried significantly increased risk for developing late-onset disease, whereas sibling asthma showed a similar but statistically nonsignificant trend. Family history of rhinitis ($P = .010$; odds ratio: 1.88; 95% confidence interval: 1.16–3.06) also emerged as a significant risk factor, although individual maternal, paternal, and sibling rhinitis did not reach statistical significance. No significant effect of breast or formula feeding was observed. Early-life pet exposure showed no trends with regard to developing late-onset persistent wheeze. Cord IgE did not vary significantly between

late-onset wheeze and never wheezing (median: 0.1 vs 0.1; $P = .166$, Mann-Whitney U test).

Adjusted Risk Factors for Early- and Late-Onset Persistent Wheeze

For obtaining the independent effect of early-life risk factors for having early-onset persistent wheeze compared with never wheezing, logistic regression analysis was used. In the final regression model, parental smoking at 2 years, chest infections at 1 or 2 years, eczema at 2 years, food allergy at 4 years, atopy at 4-year skin-prick testing, maternal urticaria, maternal asthma, and sibling asthma all showed independent significance for early-onset persistent disease (Table 3). Alternatively, high social class at birth retained a significant protective effect against this state. Recorded cat ownership at birth nearly demonstrated a similar protective effect in the final model ($P = .059$; odds ratio: 0.31; 95% confidence interval: 0.09–1.05).

Logistic regression analysis was also used to obtain the independent effect of early-life risk factors for the development of late-onset persistent wheeze compared with never wheezing. In the final regression model, eczema at 4 years, family history of rhinitis, atopic sensitization at 4 years, and maternal and paternal history of asthma all showed independent significance for developing the late-onset persistent wheezing state (Table 3).

DISCUSSION

Previously, characterization of early-onset and late-onset persistent wheezing states during the first 6 years of life in the Tucson Children's Respiratory Study³ demonstrated that these phenotypes bear many similarities. Recently,⁵ we confirmed strong associations with clinical allergy, atopy, and bronchial hyperresponsiveness for both states during the first decade of life in our own British cohort. Rather than being distinctive states, it is possible that these patterns of childhood wheezing are expressions of the same broadly atopic phenotype that typifies persistent childhood asthma. In this article, we therefore

TABLE 2. Univariate Risk Analysis for Development of Late-Onset Persistent Wheeze ($P < .05$)

Factor	Prevalence in Wheeze Phenotype		P Value	OR	95% CI
	Late-Onset Persistent	Non			
Atopic SPT 4 y	34.3% (23/67)	14.6% (75/515)	<.001	3.07	1.75–5.37
Eczema 1 y	12.3% (10/81)	6.3% (39/617)	.046	2.09	1.00–4.36
Eczema 2 y	17.3% (14/81)	8.4% (52/617)	.010	2.27	1.20–4.32
Eczema 4 y	19.8% (16/81)	8.9% (55/617)	.002	2.52	1.36–4.64
Maternal asthma	25.3% (20/79)	13.0% (77/592)	.003	2.27	1.29–3.97
Paternal asthma	24.1% (19/79)	13.0% (77/592)	.008	2.12	1.20–3.74

SPT indicates skin-prick test. Only factors that showed statistical significance ($P < .05$) are listed. Results describe comparison between late-onset persistent wheeze and nonwheezers with odds ratios (ORs) and their 95% confidence intervals (CI). Factors that showed trends for significance ($P > .05$ but $< .2$) were sibling asthma, individual or combined family histories of rhinitis, combined family history of urticaria, combined family history of food allergy, male sex, and early weaning (in the first 3 mo). Factors that did not show trends for significance ($P > .2$) were rhinitis (1, 2, and 4 years), food allergy (1, 2, and 4 years), family history of eczema, individual family histories of food allergy, individual family histories of urticaria, social class at birth, cat ownership (birth and 1, 2, and 4 years), dog ownership (birth and 1, 2, and 4 years), exclusive breastfeeding in first 3 months, exclusive formula feeding in first 3 months, parental smoking (birth and 1, 2, and 4 years), and recurrent chest infections (1 and 2 years).

TABLE 3. Multivariate Analysis of Early-Life Risk Factors for the Development of Early- and Late-Onset Persistent Wheeze

Risk Factor	P Value	OR	95% CI
Early onset			
Parental smoking at 2 y	.039	2.72	1.05–7.04
Social class I–III at birth	.005	0.24	0.09–0.65
Atopic SPT at 4 y	<.001	12.70	4.63–34.82
Recurrent chest infections at 1 y	.022	9.40	1.38–64.03
Recurrent chest infections at 2 y	<.001	90.50	21.76–376.42
Eczema at 2 y	.014	4.30	1.35–13.73
Food allergy at 4 y	.034	6.03	1.14–31.87
Maternal asthma	.003	5.51	1.76–17.25
Sibling asthma	.002	4.41	1.71–11.37
Maternal urticaria	.006	10.49	1.95–56.41
Late onset			
Eczema at 4 y	.006	2.95	1.36–6.38
Atopic SPT at 4 y	.005	2.74	1.36–5.52
Family history of rhinitis	.035	2.11	1.05–4.23
Maternal asthma	.010	2.71	1.27–5.80
Paternal asthma	.026	2.40	1.11–5.16

SPT indicates skin-prick test. Only significant results at the final step of the regression model (backward stepwise likelihood ratio testing) are shown. In each case, results are adjusted odds ratios (ORs) and their 95% confidence intervals (CI) comparing risk factors between the respective persistent wheeze phenotype (early or late onset) and nonwheezers. Factors included in the model for early-onset persistent wheeze were atopic SPT at 4 y, eczema at 1, 2, and 4 y; rhinitis at 1, 2, and 4 y; food allergy at 1, 2, and 4 y; maternal/sibling asthma; maternal/sibling urticaria; parental eczema; male sex social class I–III at birth; exclusive breastfeeding (first 3 mo of life); parental smoking at birth and 1, 2, and 4 y; recurrent chest infections at 1 and 2 y; cat ownership at birth and 4 y; and dog ownership at birth and 2 and 4 y. Factors included in the model for late-onset persistent wheeze were atopic SPT at 4 y; eczema at 1, 2, and 4 y; maternal/paternal/sibling asthma; family history of rhinitis; family history of asthma; family history of urticaria; family history of food allergy; male sex, and early introduction of solids (first 3 mo).

addressed the question of why 1 group of children experiences symptoms from infancy onward whereas the other is initially asymptomatic with problems developing only during later childhood. Our findings indicate that genetic predisposition toward developing asthma or atopy is paramount to both states but that environmental exposures in early life may facilitate earlier symptom onset.

In the Tucson cohort,³ phenotypes were defined for the first 6 years of life using a cutoff of age 3 years to define early- or late-onset wheezing. In our study, phenotypes have been defined over the first decade of life using 4 years as the boundary for early or late onset. Nevertheless, the observation that genetic influences are highly significant associations with development of persistent childhood wheezing regardless of symptom onset emerges from both studies. However, work by Rusconi et al¹⁰ using a cutoff of 2 years to define early- or late-onset wheeze demonstrated greater influence of maternal asthma on early-onset persistent wheeze. In our population, maternal urticaria plus maternal and sibling asthma conferred independently increased risk of early-onset persistent wheeze, whereas family history of rhinitis plus maternal and paternal asthma gave a significant risk of late-onset persistent wheeze. In the Tucson study, maternal asthma was a significant association for both wheezing patterns, whereas Hispanic ethnic background had a significant effect for having early-onset persistent wheeze.

Lowe et al¹¹ suggested significant interaction between maternal asthma, child's atopic status, and lung function in early childhood. In our study and that of Rusconi et al, allergic comorbidity and mater-

nal asthma emerged as strong risk factors for persistent wheezing states. Atopic sensitization at 4 years had highly significant associations for both early- and late-onset disease in our children. The German Multicenter Asthma Study¹² showed that early-life development of food allergen sensitization is of importance for subsequent significant wheezing and asthma. Our results demonstrated that allergic states in infancy (eczema, food allergy) indeed showed independent significance for early-onset persistent wheeze but not for late-onset persistent wheeze. Only conditions during a "later phase of early childhood" (at 4 years) showed such effects for late-onset persistent wheeze. Therefore, coexistent allergic disease expression seems to be intrinsically associated with timing of wheezing onset. This offers another dimension to the evolving concept of an "allergic march" during childhood whereby conditions such as eczema^{13–15} and food allergy^{12,16,17} are thought to predispose to subsequent respiratory allergy in later childhood. Coexpression of wheezing and other allergic states may simply reflect that these are clinical expressions of a common genetic predisposition. We have shown that a combination of such predisposition with environmental factors influences symptom onset.

Various environmental exposures in early life have been linked to childhood wheezing. Thus, respiratory syncytial virus infection¹⁸ in early life and environmental tobacco smoke exposure^{19–21} have been shown to be important in this context. When considering early-life environmental influences on early- and late-onset persistent wheeze in our study, a clear pattern is observed. Early-life factors such as recur-

rent chest infections, low social class at birth, and parental smoking exerted independent associations with early-onset but not late-onset persistent wheeze development. In fact, no environmental factors demonstrated significance even at univariate analysis with regard to late-onset persistent wheeze.

Previous workers have shown protective effects of breastfeeding^{22,23} against childhood wheeze. Recent findings reported from the Dunedin cohort²⁴ have failed to corroborate such effects. We noted a protective effect at univariate analysis of breastfeeding against early-onset persistent wheeze (who also showed increased disease risk with formula feeding and early weaning). No such association was found for late-onset persistent wheeze at univariate analysis. Infant feeding failed to retain independent significance for early-onset wheeze in our study at multivariate testing, reflecting interaction with other factors studied. In our population, it was shown previously⁶ that mothers of low social class smoke more and breastfeed less.

It is plausible that the early-life environmental influences that we identified superimpose on an underlying genetic predisposition to persistent wheezing and result in the earlier expression of persistent wheezing during early life. One could speculate that this is particularly so with regard to recurrent infantile chest infection given its strong associations with early-onset persistent wheeze in our cohort. The role of such infections in the inception of some forms of childhood asthma has been described previously.^{25,26} Thus, among predisposed individuals, exposure to specific pathogens during a phase of immune and structural maturation within the airways might facilitate early wheeze expression. Can we use such information to prevent development of a wheezing phenotype associated with significant disease morbidity in childhood? Prompt treatment of chest infections in infancy may offer a worthy intervention. We do not know the precise cause of the recurrent chest infections that our children experienced in infancy, but it is likely that viral pathogens were heavily implicated. Although antibiotics may not be effective in this context, antiviral therapy may hold some promise.²⁶ It also seems that alteration of early-life environment to improve socioeconomic conditions and lower environmental tobacco exposure may afford benefit.

Early- and late-onset persistent wheezers clearly possess a significant genetic predisposition to their disease. If environment is responsible for earlier expression of a predominantly genetically determined asthmatic phenotype as an early-onset persistent wheezer, then the effectiveness of trying to manipulate that environment may be questionable. When a genetically predisposed individual fails to experience the constellation of genetic and environmental influences in early life that result in early-onset persistent wheeze, it is conceivable that they might simply manifest as a late-onset persistent wheezer. Might correction of factors such as early-life smoking exposure, recurrent chest infections, and social deprivation merely delay the inevitable onset of childhood asthma (as a late-onset persistent wheezer

rather than an early-onset persistent wheezer) in a predisposed child? Future work should consider this question.

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REQUEST FOR INFORMATION: ACUTE ENCEPHALOPATHY ASSOCIATED WITH INFLUENZA VIRUS INFECTION IN US CHILDREN, 2003–2004

Since the mid-1990s, several hundred cases of acute encephalopathy have been reported in Japanese children with influenza.^{1,2} These illnesses have been characterized by fever and rapid onset of encephalopathy, resulting in a high frequency of neurologic sequelae and mortality. Most of the children have had laboratory-confirmed evidence of influenza virus infection. Reports of influenza-associated encephalopathy have been uncommon in the United States.^{3,4}

To determine if a similar pattern of influenza-associated encephalopathy is occurring in the United States, the Centers for Disease Control and Prevention (CDC) is requesting information from health care providers on any patient with acute encephalopathy meeting the following criteria during the 2003–2004 influenza season:

- <18 years old
- Altered mental status or personality change in patient lasting 24 hours and occurring within 5 days of the onset of an acute febrile respiratory illness
 - Laboratory or rapid diagnostic test evidence of acute influenza virus infection
 - Diagnosed in the United States

Please report any suspected cases to either Dr. Tim Uyeki (404-639-0277; tmu0@cdc.gov) or Dr. Niranjana Bhat (404-639-2893; nib9@cdc.gov) at CDC.

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Does Environment Mediate Earlier Onset of the Persistent Childhood Asthma Phenotype?

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