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Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia

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Abstract

Data on five allergic conditions were abstracted from the medical records of 180 cases of childhood acute lymphoblastic leukaemia (ALL) and 718 matched controls. Odds Ratios (OR) and 95% Confidence Intervals (CI) were estimated for composite variables and for individual allergies using conditional logistic regression modelling. Allergies were divided into late and early diagnoses (those made within the year before the matched case's ALL diagnosis and those made earlier, respectively). Among the early diagnoses, atopy or hives was significantly associated with ALL (OR = 2.20; 95% CI: 1.16–4.16). Significant associations were found for late diagnoses of atopy or hives (OR = 3.78; 95% CI: 1.00–14.29) and of asthma (OR = 3.10; 95% CI: 1.39–6.95). None of the other allergic conditions were associated with ALL. These results are contrary to those of prior studies of childhood ALL and allergy.

Keywords: Case–control study; Childhood leukaemia; Allergy

1. Introduction

There has been wide interest in the subject of allergy and cancers of all types. The evidence has tended to support a protective effect of allergy with adult cancers, although contradictory evidence also exists [3,10,17]. Studies of childhood leukaemia and allergy have reported mostly inverse associations [11–14,18]. We collected data from medical records on five allergic conditions in the course of a case–control study of vaccination and acute lymphoblastic leukaemia (ALL). Although allergy data were collected as potential confounders in the above study, previous reports of an inverse association between allergies and ALL (above) made the examination of such an association appropriate. Moreover, uniquely among studies of childhood leukaemia, we collected the dates of allergy diagnoses and were able to classify them into those made much earlier than the date of ALL diagnosis, those made closer to the ALL diagnosis, and those made after the diagnosis. That is, we were able to differentiate between time periods that were probably, possibly aetiologically relevant, and those that were definitely not, respectively. We present here, our study of medically recorded allergies and the risk of childhood ALL.

2. Patients and methods

We identified cases and controls through the databases of four health maintenance organisations (HMOs) in the Western United States: Kaiser-Permanente

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Health Systems in Southern and Northern California and Oregon (SCK, NCK, and NWK, respectively), and the Group Health Cooperative (GHC) of Puget Sound. These four HMOs contribute data to the Vaccine Safety Datalink Project, which is sponsored by the National Immunization Program of the Centers for Disease Control and Prevention [2]. Cases were children aged 6 years or younger who were diagnosed with ALL (International Classification of Diseases (ICD)-9 code 204.0) between 1985 and 1999, and born in 1983 or later. A pathologist, blinded to the exposure status, reviewed case laboratory reports to confirm a diagnosis of ALL and, when possible, to classify the subtype of ALL into B- or T-cell lineages. Controls were individually matched to cases on HMO, gender and date of birth (within 2 weeks) and, in addition to meeting the eligibility criteria, must have been enrolled at the time of the matched case's diagnosis. To be eligible, subjects must have enrolled in their HMO within 90 days of birth (extended to 180 days at the Southern California Kaiser) and must have been continuously enrolled up until the earlier of either the matched case's date of diagnosis or 2 years of age. Professional abstractors employed by the HMOs collected information regarding demographics (race, ethnicity, sibship and gender), birth variables (birth weight, gestational age and maternal age at birth of subject), and vaccination history from the subject's medical charts. Five categories of allergies—asthma, atopy or hives, eczema, food-drug-bee allergy (FDBA), and pollen-dust-dander allergy (PDDA)—and the dates of their first diagnosis were also recorded. Allergies were recorded if they were diagnosed by a physician, either within the HMO or without, and had a month and year of diagnosis. Day was assigned a value of 15 if missing. Subjects were presumed not to have an allergic condition if no mention of diagnosis was made in the medical chart.

Breast feeding, maternal age, birth weight, sibship, and race were considered as potential confounders. The continuous covariates—birth weight, maternal age and sibship—were dichotomised. These variables, as well as breast feeding and race, were given an additional category that indicated missing data. Models in which observations were dropped that were missing data did not produce markedly different allergy point estimates than those including indicator variables for missing data. Therefore, we allowed observations with missing covariate data to remain in the models. Covariates were dichotomised as follows: Mother's age (<35 years, 35 years+), birth weight (<3500 g, 3500 g+) and sibship (0, 1+ siblings). P values for the difference in the means of covariates were calculated using the two-sample test for proportions.

Odds Ratios (OR) were calculated by conditional logistic regression using SAS PROC PHREG (version 8.2, SAS Institute, 2001). Each subject was assigned an index date, which for cases was the date of diagnosis of ALL and for controls was that of the matched case. In order to discern any latent period effects, which are of interest in themselves, we divided allergies into those diagnosed within 1 year before the index date (late diagnosis) and those diagnosed 1 year or more before the index date (early diagnosis), and ignored allergies diagnosed after the index date. Although the length of the latent period is not known, 1 year is a reasonable estimate based on mathematical modelling of ALL incidence [15]. We analysed three separate models with allergy variables: two with composite allergy variables (any allergy and number of allergies) and a multivariate model with the individual allergy diagnoses. The potential confounders described above were entered into each of these three models, and were then dropped from the models if, upon inspection, they did not change allergy point estimates meaningfully [8].

We conducted these analyses in parallel for both the matched sets of all cases and the subset of matched sets of presumptive B-cell cases (confirmed B-cell lineage plus unknown lineage ALL, ages 1.5–6 years). The lower age limit of 1.5 years was chosen to allow at least a 6-month window during which early allergies may have been diagnosed. Analysis of the presumptive B-cell subset was of interest since the different immunophenotypes of ALL are thought to have different aetiologies. Although approximately one-third of cases were of unknown lineage, the ratio of B- to T-cell lineage cases among cases of known lineage, 7.5:1, was in the expected range for an industrialised country (e.g. one survey found that the ratio of common ALL to T-cell lineage ALL was 5 in the UK and 9.5 in Australia and New Zealand) [5]. Because of this, and because the age distribution of the unclassified cases was dissimilar to that of the confirmed T-cell lineage (Table 1) cases, we therefore presume that most unclassified cases were not T-cell lineage ALL and included them with known B-cell cases in the subset for analysis.

3. Results

We identified 180 eligible cases of ALL, 147 of which were of presumptive B-cell lineage. The ratio of controls to cases was originally 4:1, but two controls were discovered to be ineligible and were excluded, resulting in 718 controls (586 in the presumptive B-cell sub-set). Most cases (56.1%) were male and the mean age at diagnosis was 3.15 years (S.D. 1.50 years; range 0.23–6.86 years). While cases were less often black than the controls, maternal age, birth weight, breast feeding, and sibship were similar among cases and controls without missing values (Table 2). The proportions of cases and controls missing values for maternal age and birth weight were similar, while controls were significantly

Table 1
Cell type and age at diagnosis of ALL cases

Cell type	Age at diagnosis								
	0 y (*n*)	1–1.5 y (*n*)	1.5–2 y (*n*)	2 y (*n*)	3 y (*n*)	4 y (*n*)	5 y (*n*)	6 y (*n*)	Total
B	8	7	7	31	19	21	2	10	105
T	2	0	3	1	2	3	1	2	14
Unknown	2	2	7	24	18	5	3	0	61
All	12	9	17	56	39	29	6	12	180

ALL, acute lymphoblastic leukaemia; y, years; *n*, number.

Table 2
Characteristics of cases and controls

	Cases $N=180$ (%)[a]	Controls $N=718$ (%)[a]	P value[b]
HMO			
NCK	70 (39)	280 (39)	
SCK	85 (47)	340 (47)	
NWK	12 (7)	48 (7)	
GHC	13 (7)	50 (7)	
Gender			
Male	101 (56)	402 (56)	0.98
Female	79 (44)	316 (44)	
Race			
White	92 (52)	301 (52)	0.95
Black	12 (7)	72 (12)	0.04
Other	73 (41)	207 (36)	0.19
Age of mother (years)			
<35	107 (78)	433 (82)	0.26
$\geqslant 35$	30 (22)	93 (18)	
Birth weight (g)			
<3500	72 (43)	334 (49)	0.59
$\geqslant 3500$	95 (57)	341 (51)	
Breast fed			
Yes	115 (76)	493 (73)	0.58
No	37 (24)	178 (27)	
Any older siblings			
Yes	103 (67)	435 (67)	0.96
No	50 (33)	213 (33)	

[a] Percentage of known values; 61 (34%) cases missing cell type; 3 (2%) cases and 138 (19%) controls missing race; 43 (24%) cases and 192 (27%) controls missing age of mother at birth; 13 (7%) cases and 43 (6%) controls missing birth weight; 28 (16%) cases and 47 (7%) controls missing breast feeding history; 27 (15%) cases and 70 (10%) controls missing sibship.

[b] Derived from two-sample test for proportions comparing cases and controls without missing values of variable. P values for race compare each category against the other two categories combined.

more often missing values for race and cases were significantly more often missing values for sibship and breast feeding history (data not shown).

Table 3 shows the results of conditional logistic regression. There was no significant association of ALL with combined allergic conditions diagnosed early in either the set of all cases or the set of presumptive B-cell cases. Combined allergic conditions diagnosed late showed a significant direct association with ALL in the set of all cases (OR: 1.84; 95% CI: 1.02–3.33), but not in the subset. There was an apparent, but non-significant, trend ($P=0.10$ in the set of all cases, $P=0.15$ in the set of presumptive B-cell cases) with the number of allergic conditions diagnosed early, with odds more than doubled in the 3+ category. No trend was apparent for the number of late diagnoses of allergies.

The odds of ALL were significantly raised in children with an early diagnosis of atopy or hives, with ORs of 2.20 (95% CI: 1.16–4.16) in the set of all cases and of 2.02 (95% CI: 1.03–3.96) in the presumptive B-cell set. None of the other early diagnoses of allergic conditions exhibited a significant association with ALL. Atopy or hives and asthma, diagnosed in the year prior to the index date, both showed significant associations with ALL in the set of all cases, while only asthma did so in the set of presumptive B-cell cases. The OR was 3.78 (95% CI: 1.00–14.29) for atopy or hives and 3.10 (95% CI: 1.39–6.95) for asthma in the set of all cases. The OR for asthma was 3.38 (95% CI: 1.31–8.72) in the set of presumptive B-cell cases. The OR for late diagnoses of atopy or hives was 3.73, but only 11 children had these within the year before diagnosis.

When we restricted analysis to confirmed B-cell cases and their matched controls, point estimates were similar, but less precise, than those from the set of presumptive B-cell cases. For instance, the ORs (95% CI) for having one, two, and three early diagnoses of allergy were 1.32 (0.75–2.32), 1.65 (0.60–4.50), 2.10 (0.39–11.25), respectively (other data not shown). Excluding from the analysis five matched sets in which the case had Down syndrome did not materially affect the results reported above (data not shown).

4. Discussion

The results of this study are not consistent with those of five previously reported studies of this topic, each of which found inverse associations of allergy and childhood ALL, three were significant [11–14,18]. The three studies that analysed individual allergies found significant inverse associations with asthma, hay fever, FDBA, PDDA, neurodermatitis and eczema. In contrast, one

Table 3
Childhood ALL and allergic conditions adjusted for age, gender, race and HMO[a]

	All cases		Presumptive B-cell cases	
	Cases (180)/ controls (718)	OR (95% CI)	Cases (147)/ controls (586)	OR (95% CI)
Composite variable models				
Combined allergic conditions				
Dx ⩾1 year before index date	48/173	1.24 (0.82–1.86)	44/158	1.22 (0.79–1.87)
Dx <1 year before index date	21/53	1.84 (1.02–3.33)	15/39	1.68 (0.85–3.30)
Number of allergies Dx ⩾1 year before index date				
1	34/132	1.11 (0.71–1.75)	31/121	1.09 (0.68–1.75)
2	9/33	1.40 (0.62–3.17)	9/29	1.52 (0.66–3.49)
3+	5/8	2.90 (0.90–2.61)	4/8	2.39 (0.67–8.50)
Trend *P* value[b]		0.10		0.15
Number of allergies Dx <1 year before index date				
1	20/48	1.94 (1.05–3.57)	14/35	1.73 (0.85–3.52)
2	1/5	0.56 (0.05–5.87)	1/4	0.68 (0.06–7.30)
Trend *P* value[b]		0.11		0.26
Multivariate models				
Asthma[c]				
Dx ⩾1 year before index date	18/57	1.56 (0.85–2.87)	18/57	1.59 (0.83–3.04)
Dx <1 year before index date	13/21	3.10 (1.39–6.95)	10/16	3.38 (1.31–8.72)
Atopy or hives[c]				
Dx >1 year before index date	19/45	2.20 (1.16–4.16)	16/41	2.02 (1.03–3.96)
Dx <1 year before index date	5/9	3.78 (1.00–14.29)	4/7	3.73 (0.86–16.2)
Eczema[c]				
Dx >1 year before index date	20/62	1.09 (0.60–1.96)	19/62	1.12 (0.61–2.04)
Dx <1 year before index date	0/14	0.00 (0.00–undefined)	0/12	0.00 (0.00–undefined)
FDBA[c]				
Dx >1 year before index date	8/44	0.65 (0.28–1.51)	8/41	0.70 (0.30–1.65)
Dx <1 year before index date	4/14	1.24 (0.35–4.42)	2/8	0.94 (0.19–4.77)
PDDA[c]				
Dx >1 year before index date	3/10	1.13 (0.25–5.15)	3/10	1.11 (0.24–5.20)
Dx <1 year before index date	0/0		0/0	

Dx, diagnosis; FBDA, food-drug-bee allergy; PDDA, pollen-dust-dander allergy; OR, odds ratios; 95% CI, 95% Confidence Intervals.
[a] No allergy is referent for all variables.
[b] *P* value from treating number of allergies as a continuous variable.
[c] Mutually adjusted.

study reported significant direct associations of family history of allergy; these associations appeared to be confined to the pre-B and T-cell ALL subtypes [1].

A major strength of the present study is that we obtained dates of diagnoses of allergies from medical records. Thus, we were able to ensure that the allergies preceded the diagnosis of ALL and to account for the latent period. Previous case–control studies collected allergy information by parental interview or questionnaire and were not able to be as precise. They may have included allergies that occurred during the latent period of ALL or even after diagnosis, which would not be aetiologically relevant. Control parents would be more prone than case parents to report allergies diagnosed past the index date since they lack the clear reference point of a diagnosis of ALL in their child, and this would drive allergy ORs downwards. Schuz and colleagues [14] found evidence of this sort of bias in their study of allergy and ALL. They reported that the percentage of controls' parents reporting allergy in their children increased and, unexpectedly, the percentage of cases' parents reporting allergy in their children *de*creased with a greater length of time between the index date and interview. Controlling for the time between the index date and interview considerably diminished the evidence that allergy was inversely associated with ALL. A similar bias may have operated in previous studies which had similar methodologies, and may explain at least part of the discrepancy between them and the current study.

We estimated a latent period of ALL of 1 year and described the occurrence of allergies during this time. Rather than contributing to the development of disease, exposures that occur during the latent period may be a consequence of preclinical ALL. Atopy or hives were more common among cases than among controls both before and during the latent period, whereas diagnoses of asthma were more common among cases only within the year before the index date. Thus, the evidence for a causal association with ALL is stronger for atopy or hives than for asthma. Instead, the evidence suggests that perhaps leukaemia predisposes to asthma.

Reliance on chart documentation of allergy may have reduced sensitivity in detection, since we could not document allergies that were not diagnosed and recorded by a physician. Researchers have documented that mothers report more infections in their children than doctor records indicate [9], and the same process may work for allergies. However, this misclassification should not be a differential for cases and controls. Abstractors, while not blinded to case and control status, were not told of any hypotheses regarding allergy and ALL and so should not have been a source of bias. Our results could have come about if diagnoses of allergies were mentioned at the time of the leukaemia diagnosis and noted by a physician. Since controls would not receive a similarly thorough questioning about their medical history this could be a source of bias. However, since a date of diagnosis would probably not be given for allergies recorded in this way and we analysed only those allergies that had a date of diagnosis, bias of this type is likely to be minimal.

In addition, as a result of relying on chart documentation, a number of potential confounders were missing. The variables that were missing non-differentially should not arouse concern. That cases were much less often missing race is easily explained—with many more doctor's visits, there was more opportunity for a chart of a case to mention race. No explanation is apparent for why cases were more often missing breast feeding history and sibship, but the lack of difference in allergy point estimates in models in which observations were dropped that were missing data and models that included indicator variables for missing data provides reassurance that missing covariate data were not a source of bias.

Another possible explanation for our results is confounding by a factor for which we were not able to control. We were limited to collecting data available in medical charts, which rarely contain data on two known correlates of risk of ALL: maternal education or income. However, the socioeconomic status tends not to be highly variable in the HMOs from which subjects were drawn [4]. Other strong, consistent risk factors for ALL have not been identified. Thus, it is difficult to imagine an undiscovered risk factor for ALL that could account for our results. Furthermore, if we assume that previous inverse associations are real, it is especially difficult to imagine any factor that could confound allergy to the point of crossing over to a point estimate of 2.

Lastly, we cannot rule out the possibility that chance explains our results. If we consider the number of comparisons made in our analysis and apply a Bonferroni correction [7], the findings regarding atopy or hives and asthma would not be significant (data not shown). Nevertheless, even the finding of a null association of allergies with ALL contrasts with previous studies.

These data indicate a direct association of atopy or hives with childhood ALL. If true, the relationship may not be causal, but rather it may reflect a common pathway in the aetiology of both allergy and ALL. Evidence has accumulated, but is not yet conclusive, that both atopy and ALL result from a relative lack of exposure to infections in early childhood [6,16]. Thus, it is plausible that atopy is a marker for early patterns of infection. The study presents a stark contrast to previous findings of a protective association of allergy with childhood ALL.

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