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Allergy and risk of acute lymphoblastic leukemia among children: A nationwide case control study in Greece

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ABSTRACT

Background: Several reports point to inverse associations between allergies and ALL; yet, no study has explored this link using both self-reported-data on allergic history and biomarkers of atopic sensitization. **Methods:** Clinical information for the variables of interest was available for 252 out of 292 cases of childhood (0–14 years) ALL, newly diagnosed across Greece over a 4.5 year period as well as for 294 hospital controls. Allergen-specific-IgEs, as markers of allergic predisposition, against 24 most prevalent respiratory and food allergens, were determined, using an enzyme immunoassay procedure for 199 children with ALL and 113 controls. Cases were compared with controls through frequency distributions and unconditional multiple logistic regression models to estimate odds ratios (ORs) and 95% confidence-intervals (CIs) regarding associations of allergy with childhood ALL. **Results:** Self-reported-allergic history overall (OR: 0.49, 95%CI: 0.34–0.72) and practically each one of its main components (respiratory, food, any other clinical allergy) were strongly and inversely associated with ALL. Likewise, the serum IgE inverse association was of the same magnitude (OR: 0.43, 95%CI: 0.22–0.84) mainly contributed by food IgE (OR: 0.39, 95%CI: 0.18–0.83). **Conclusion:** Beyond the already established inverse association of allergic history with childhood ALL, a same magnitude association is evident when serologic markers of allergic predisposition are used as an alternative measure of allergy. Further research with more appropriate study designs is needed to better understand possible associations between prior allergy and childhood ALL risk.

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1. Introduction

Leukemia represents one third of all malignancies among children (0–14 year old), with acute lymphoblastic leukemia (ALL), the predominant histological type, accounting for >80% of all leukemias [1]. Incidence of childhood lymphoblastic leukemia, including acute lymphoblastic leukemia, has been reported to have increased significantly in several European countries during the period 1970–1999 by an average of 1.4% per year [2], and 0.7% in

the USA [3] whereas some investigators report no significant changes in the incidence of childhood leukemia overall or by leukemia subtypes, especially during the most recent decades [4–8]. During a later period (1996–2006) for which data are available in Greece, an increasing secular trend in the incidence of the disease has been found; of note, childhood leukemia incidence in Greece (46.60 cases per 1 million children annually) is 19% higher than the average and among the highest in the 27 European Union member states [9]. Part of the reported rise in ALL incidence might be attributed to advanced diagnostic techniques and cancer registration methods [10], yet changing lifestyle [2,8] and environmental exposures might also play a role [11,12].

The etiology of childhood leukemia remains rather obscure, with both genetic susceptibility and environmental factors being implicated [13–19]. Allergic diseases such as eczema, hay fever and

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asthma, originating from an aberrant immune response to innocuous environmental antigens, have also been reported to increase worldwide, as well as among Greek children, during the late 20th century [20–24]. The rising incidence of both conditions during the late 20th century might point to environmental risk factors that could be shared for both allergic disorders and leukemia. A possible infectious agent could be the missing link of the equation, despite the fact that the role of early infections in ALL and asthma risk is highly debated. Indeed, some reports in favor of the “hygiene hypothesis”, are showing that intense early-life exposure to a range of infectious agents acts protectively against both childhood asthma [25], as well as childhood leukemia [26–29], whereas other studies have demonstrated significant positive associations [30] or no association [31] between ALL and infections of the upper respiratory tract during infancy. With regards to asthma, epidemiological data from various studies showed that RSV [32,33] and rhinovirus infections [34,35] can enhance allergic sensitization.

History of allergy is commonly used as a proxy of a germ-deficient childhood environment that is likely to be protective against the risk of childhood leukemia or ALL, in particular [28,29,36–42]. In most of the published studies, however, exposure assessment was estimated via retrospective review of medical records and/or parental report of allergic history, introducing several potential sources of misclassification or recall biases. To our knowledge, no previous study has investigated the reported link between allergy and ALL, using both self reported data on allergic history as well as laboratory confirmation of allergic status. In the current case control investigation, comprising childhood leukemia incidence cases derived from the Nationwide Registry for Childhood Hematological Malignancies (NARECHEM) in Greece and hospital controls, we sought to explore the individual as well as joint effect of allergen-specific (IgE) antibodies levels and self reported allergic history in the etiology of the disease [43]. To this end, we have opted to use both self reported data on allergic history as well as laboratory confirmation of allergic status.

2. Materials and methods

During the 4.5 year period (1/1/1999 to 30/6/2003) detailed interview data were available for 338 incident childhood ALL cases, diagnosed in all six pediatric hematology-oncology departments across Greece and contributed to NARECHEM [43]. During the study period one of the two centers reporting from Thessaloniki did not avail detailed questionnaires for its 46 ALL incident cases; as this exclusion was only due to administrative reasons, it is not likely to have introduced any sort of bias [44]; Moreover the 46 excluded ALL cases did not significantly differ in distribution of sex age and immunophenotype with the rest of the study sample (data not shown). Gender and age (± 6 months) matched controls derived also from pediatric hospitals among those admitted for pediatric ailments such as minor respiratory conditions or viral infections, febrile seizures, gastrointestinal or genitourinary conditions and accidental poisonings at the same time as the corresponding cases. Eventually, 23 control children with atopic admission diagnoses were excluded for the purpose of this study. This was performed in order not to bias control selection in favor of the hypothesis under study, namely that allergic children were less likely to develop NHL. No history of malignancy or chronic disease was reported in the control series. Informed consent was obtained by the guardians of all children and the study protocol was approved by the Ethics Committee of the Athens University Medical School.

The guardians of cases and controls were interviewed in person on the basis of a structured questionnaire covering socio-demographic, anthropometric, perinatal and medical history characteristics. In addition, detailed information regarding past

history of asthma, allergic rhinitis, eczema, and hives were collected. Moreover, the children's guardians were asked to report whether the index child had ever used prescribed nasal, inhaled or oral corticosteroids, antihistamines and bronchodilators. Food or medication allergy and the allergic reaction type were also documented. All answers were recorded and later grouped to the following categories: respiratory allergy (asthma and allergic rhinitis), food allergy and other allergies (eczema, medication allergy, hives not attributed to drug or food allergens).

Among the remaining 292 cases, information in the detailed allergic history questionnaire was not available for 40 ALL eligible cases (86% response rate), whereas among the 315 eligible controls, 21 did not provide an allergy questionnaire (93% response rate). Fasting blood samples were collected during routine clinical procedures before the initiation of therapy from all cases and controls (no later than 09:00 a.m.); the interview followed shortly after the establishment of a trust relation with the treating physician. Thus, for ALL cases and their respective controls, the child's age represents the age at diagnosis which was practically the same time of blood draw and completion of the questionnaire. NARECHEM blood samples have been previously used for a series of studies [44]; for the current investigation blood samples were available for 199 children with ALL and 113 controls.

Coded, frozen samples were transferred to the Department of Immunology and Histocompatibility of the University of Thessaly Medical School in Larissa, where allergen-specific IgE levels were determined using an enzyme immunoassay (EIA) (Hytec, Hycor). To determine the allergen-specific IgE antibodies, blood samples were centrifuged and the sera obtained were stored at -70°C blinded as to case-control status. The sensitivity of the assay was 0.35 IU/ml and the intra-assay coefficient of variation was 7%. In particular, serum levels of specific IgE antibodies against the 24 most prevalent respiratory and food allergens were measured. The respiratory IgE panel included 3 mixtures (ex2, hx2, mx1) of 4 common allergens each: ex2 mixture of: e1 – cat epithelium and dander, e2 – dog epithelium, e6 – guinea pig epithelium, e84 – golden hamster epithelium, hx2 mixture of: h2 – house dust (Hollister strier), d1 – dermatophagoids pteronyssinus, d2 – dermatophagoids farinae, i6 – cockroach and mx1 mixture of: m1 – penicillium notatum, m2 – cladosporium herbarum, m3 – aspergillus fumigatus, m6 – alternaria tenuis. The food panel (fx1 and fx5) included 12 allergens that compromise most food allergies (milk, egg, codfish, wheat, soybean, strawberry, celery, peanut, hazelnut, brazil nut, almond, coconut). Respiratory and food IgE were categorized into two groups: <0.35 IU/ml = negative and ≥ 0.35 IU/ml = positive. Positivity to one or more of the allergens tested was defined as evidence of allergy. Samples of both cases and controls were analyzed at the same day, in the same manner, while the laboratory technicians were blinded to case/control status.

Frequency distributions for ALL cases compared to their controls by the study variables were initially generated, using Chi-square tests for trend or contrasts. Subsequently, unconditional multiple logistic regression models were developed using case/control status as the outcome variable, whereas allergic history and specific IgE positivity served as the predictor variables. Control for a series of potential confounders included age, gender, maternal education (one level more), maternal age at birth (5 years increment), breastfeeding duration (2 months increment), maternal smoking during pregnancy (yes vs. no), birth weight (500 g increment), birth order (1 more increment). The SAS statistical package (SAS Institute Inc., NC, USA) was used in all analyses [45].

3. Results

The distribution of cases and controls by socio-demographic, anthropometric and perinatal variables is shown in Table 1. The

Table 1

Distribution of the 252 acute lymphoblastic leukemia cases and 294 controls by socio-demographic and perinatal variables.

Variable, category or increment	Cases		Controls		p-Value for trend (*) or contrast (**)
	N	%	N	%	
Age, years					0.05*
<5	136	54.0	142	48.3	
5–9	80	31.7	88	29.9	
10+	36	14.3	64	21.8	
Gender					0.84**
Male	147	58.3	169	57.5	
Female	105	41.7	125	42.5	
Maternal education, years					0.21**
<10	83	33.0	73	24.8	
10–12	113	44.8	157	53.4	
13+	56	22.2	64	21.8	
Maternal age at birth, years					0.77*
<20	11	4.4	12	4.1	
20–24	70	27.8	75	25.5	
25–29	76	30.1	106	36.1	
30–34	63	25.0	70	23.8	
35+	32	12.7	31	10.5	
Breast feeding, months					0.06*
No	61	24.2	62	21.1	
<2	69	27.4	58	19.7	
2–3.9	38	15.1	63	21.4	
4–5.9	35	13.9	38	12.9	
6+	49	19.4	73	24.9	
Maternal smoking during pregnancy					0.20**
No	203	80.6	249	84.7	
Yes	49	19.4	45	15.3	
Birth weight, g					0.09*
<3000	54	21.4	61	20.8	
3000–3499	97	38.5	140	47.6	
3500–3999	73	29.0	75	25.5	
4000+	28	11.1	18	6.1	
Sibship size					0.28*
One	62	24.6	72	24.5	
Two	132	52.4	168	57.1	
Three	40	15.9	41	14.0	
Four+	18	7.1	13	4.4	
Birth order					0.99*
1st	108	42.9	123	41.8	
2nd	104	41.2	127	43.2	
3+	40	15.9	44	15.0	

data serve mostly descriptive purposes and are not directly interpretable because of mutual confounding. As expected, however, cases tend to be born with heavier birth weight. The 199 cases with readily available blood samples did not significantly differ in distribution of age, sex and self reported allergy data with the rest of the 252 ALL cases (data not shown). Table 2 shows the distribution of cases and controls by reported allergic history as well as by allergen specific IgE levels. Likewise, these data are not directly interpretable. As expected, they show statistically significant inverse associations of ALL with a reported history of allergy, namely respiratory, eczema, hives or drug allergy as well as the serum IgE-specific positivity overall and food allergens, in particular. Regarding the associations of any clinical and or IgE reactivity, the results are essentially driven by the inverse associations noted in the individual analyses.

We have estimated the concordance for both cases and controls regarding clinical and laboratory data. The relevant figures between self-reported food allergy and food IgE levels among both cases and controls were 87%, whereas the respective feature for respiratory allergens was 83%. Concordance between self reported food allergies and food IgEs was 92% for cases and 80% for controls (p -value 0.003). Concordance between self reported respiratory allergies and respiratory IgEs was 84% for cases and 81% for controls (p -value 0.57).

In Table 3, results of the unconditional multiple logistic analysis regarding the association of ALL with self reported allergic history and laboratory confirmed IgE-specific positivity to a series of allergens, including respiratory or food, are shown after adjustment with possible confounders. Concerning socio-demographic and lifestyle variables, the results are in line with previously published studies [37]. The expected inverse association of self-reported allergic history overall with ALL is confirmed in this study (OR: 0.49, 95%CI: 0.34–0.72) and practically each one of its main components (respiratory, food, any other clinical allergy). Likewise, the serum IgE inverse association was of the same magnitude (OR: 0.43, 95%CI: 0.22–0.84) and seemed to be mainly contributed by food IgE (OR: 0.39, 95%CI: 0.18–0.83). The same results were derived when either clinical allergic history or IgE overall or by subtype (food or respiratory) were jointly introduced in the model.

4. Discussion

A strong and statistically significant inverse association of ALL risk with both serum IgE-reactivity overall (OR = 0.43) and food allergens in particular (OR = 0.39) as well as with the allergic history reported by the child's guardians was found for the first time in this case control study. The findings are rather robust, although the study design does not allow exploring whether the association is causal in nature.

Inverse association of clinically reported allergy with ALL: The low concordance between self reported food allergies and food related IgEs seems in line with the published literature [46]. Indeed, much of the discordance among cases and controls (self-report false positives) might probably reflect non allergic food hypersensitivity, an allergy that was surpassed or extended allergen avoidance. Self-report false negatives might be the result of food sensitization, either hypoclinal or not acknowledged by the mothers as a type of allergy [46]. Overall, the results regarding the association of clinically reported allergy with ALL, are consistent with findings from other case-control studies [28,29,36–42] suggesting that the combined history of allergic disorders evaluated among cases was associated with a significant reduced risk of ALL. This reduced likelihood of leukemogenesis among children with a household history of allergy in the latter studies could be suggestive of the shared genetic and environmental determinants in a family that both affect the manifestation of allergic disorders and ALL.

Inverse association of allergy biomarkers with ALL: Serum IgE measurement stands as a less subjective way to assess allergic predisposition and may help avoid possible biases arising through parental reporting of childhood allergy. As immunoglobulins, including IgE, however, are produced by the immune system in response to specific antigens that invade the human body, there is some skepticism whether the reported results are due to enhanced immune status in allergic controls or on account of reverse causality, namely reflecting disease immunosuppression in ALL cases. Yet, a retrospective study reports normal IgG, IgA and IgM concentration at ALL onset and normal cellular and humoral immunity values until after intense antineoplastic treatment or final disease stage [47].

The findings of the study might feature a protective association of allergy with childhood ALL; yet the link of inflammatory allergic reactions and cancer has not been thoroughly explored. Chronic inflammation triggered by environmental factors (e.g. infection, tobacco, asbestos) and/or host mutations can promote cancer development [48,49], whereas other studies show that certain inflammatory mediators (IL-1b, IL-17) may demonstrate anti-tumor functions [50,51]. Multiple studies support the notion that inducing invariant natural killer T (iNKT) cell activation can inhibit tumor progression and promote lasting tumor immunity [52]. Lastly, in animal models, airway inflammation as a feature of

Table 2
Distribution of the 252 acute lymphoblastic leukemia cases and 294 controls by reported clinical allergy history as well as of 199 ALL cases and 113 controls by serum specific IgE reactivity to respiratory or food allergens.

Allergy type	Cases		Controls		p-Value
	N	%	N	%	
<i>Reported clinical allergy</i>					
Any clinical allergy (food, respiratory, eczema, hives, medication allergy)					0.001
Negative	186	73.8	178	60.5	
Positive	66	26.2	116	39.5	
Clinical food allergy					0.07
Negative	239	94.8	267	90.8	
Positive	13	5.2	27	9.2	
Clinical respiratory allergy					0.02
Negative	222	88.1	238	81.0	
Positive	30	11.9	56	19.0	
Any other clinical allergy (eczema, hives, medication allergy)					0.03
Negative	214	84.9	228	77.6	
Positive	38	15.1	66	22.4	
<i>Serum specific IgE reactivity</i>					
Any IgE ^a					0.04
Negative	176	88.4	90	79.7	
Positive	23	11.6	23	20.3	
Any food IgE (FX1, FX5) ^a					0.03
Negative	183	92.0	95	84.1	
Positive	16	8.0	18	15.9	
Any respiratory IgE (ex2, hx2, mx1) ^a					0.45
Negative	189	95.0	105	92.9	
Positive	10	5.0	8	7.1	
<i>Clinical allergy and/or serum specific IgE reactivity</i>					
Any allergy (clinical or IgE) ^a					0.01
Negative	132	66.3	59	52.2	
Positive	67	33.7	54	47.8	
Any food allergy (clinical or IgE) ^a					0.003
Negative	178	89.5	87	77.0	
Positive	21	10.5	26	23.0	
Any respiratory allergy (clinical or IgE) ^a					0.54
Negative	164	82.4	90	79.7	
Positive	35	17.6	23	20.3	

^a Data available for 199 ALL and 113 controls.

allergic asthma was shown to require the presence of iNKT cells [53–55], providing the possible link for the inverse association of allergy and ALL.

A less plausible explanation could point to the antitumor activity of histamine [56], a chemical mediator of allergic reactions,

that protects natural killer cells and T cells against oxygen radical-induced damage and death by suppressing oxygen radical formation, and also optimizes lymphocyte activation by cytokines [57]. Clinical trials in metastatic malignant melanoma [58] and acute myeloid leukemia [58,59] have demonstrated the potential

Table 3
Unconditional multiple logistic regression-derived odds ratios (ORs) and 95% confidence intervals (95%CI) for childhood acute lymphoblastic leukemia by socio-demographic, reported allergy history and serum specific IgE reactivity to respiratory or food allergens.

Variable	Category or increment	ORs	95%CIs		p-Value
Core model					
Age	1 year more	0.94	0.90	0.99	0.02
Gender	Male	Referent			
	Female	1.00	0.70	1.42	1.00
Maternal education	1 level more	0.85	0.66	1.10	0.22
Maternal age at birth	5 years more	1.03	0.86	1.22	0.78
Breast feeding	2 months more	0.89	0.79	1.00	0.06
Maternal smoking during pregnancy	Yes vs. no	1.32	0.83	2.10	0.24
Birth weight	500 g more	1.23	1.01	1.50	0.04
Sibship size	One more	1.45	1.02	2.06	0.04
Birth order	One more	0.72	0.49	1.06	0.09
Alternatively additionally introduced variables					
Any clinical allergy	Positive vs. negative	0.49	0.34	0.72	0.0003
Clinical food allergy	Positive vs. negative	0.52	0.26	1.05	0.06
Clinical respiratory allergy	Positive vs. negative	0.52	0.32	0.86	0.01
Any other clinical allergy	Positive vs. negative	0.57	0.36	0.90	0.02
Any IgE	Positive vs. negative ^a	0.43	0.22	0.84	0.01
Any food IgE (FX1, FX5)	Positive vs. negative ^a	0.39	0.18	0.83	0.02
Any respiratory IgE (ex2, hx2, mx1)	Positive vs. negative ^a	0.62	0.23	1.72	0.36
Any allergy (clinical or IgE)	Positive vs. negative ^a	0.48	0.29	0.79	0.004
Any food allergy (clinical or IgE)	Positive vs. negative ^a	0.35	0.18	0.68	0.002
Any respiratory allergy (clinical or IgE)	Positive vs. negative ^a	0.73	0.39	1.34	0.31

^a Models with 199 ALL and 113 controls.

to improve treatment outcome when histamine dihydrochloride is combined with immunotherapy. By contrast, it has been hypothesized that in allergic individuals, antigenic stimulation subjects the immune system to a chronically hyperreactive state, leading to an inflammatory cascade of cellular and cytokine reactions that tax the host immune response, provoke tissue injury and eventually result in lymphoid neoplasia [60].

A number of studies have shown that immune system development begins in utero and may be modulated by maternal immune status [61–63]. In addition, a study exploring the influence of maternal immune status on childhood leukemia risk has revealed elevated levels of total IgE or respiratory and food IgE, in particular among mothers of children with ALL compared to control children's mothers [64]. Although the finding is rather inconsistent with the prevailing theory, on the inverse association of allergies with childhood leukemia, – given that mothers share only 50% of the genetic reservoir with their children, it can be assumed that environmental aspects can also strongly affect allergic sensitization. Finally, ALL cases may be considered as nonatopic children of atopic mothers, in the sense that a child who is genetically and environmentally programmed to develop allergy but does not, might also be unable to respond correctly to emerging cancer cells, leading to augmented hazard of leukemia development [64].

The high response rates and quality of personal interview derived information as well as the simultaneous examination of a serological marker of allergic predisposition toward a variety of the most prevalent allergens in Greece are among the strengths of the study. Moreover, personal interview reporting of relatively mild conditions as hay fever, asthma and eczema data might be more accurate in comparison to that elicited and recorded by the busy clinician in the routine medical record [65]. Compared to studies among adults, misclassification or recall bias may be expected to have been less present in the current study, as the recall period refers to a shorter (15 years) time span compared to that for adults.

The findings of the study should be interpreted, however, in light of several limitations. Information bias cannot be excluded; even if such a bias was introduced to some extent, however, this would have led to an underestimation of the strength of the association between allergy and childhood ALL risk [65]. Blood samples were available for a subset of study subjects but this is unlikely to have introduced any bias as this was due to the depletion of the respective individual biological material reservoir. Despite the nationwide coverage of NARECHEM and the over 15 years study period, the sample size is by necessity modest, due to the rarity of neoplastic diseases in children, leading to limited statistical power, an inherent limitation that could be overcome only in large consortia studies, such as the Childhood Leukemia International Consortium [66]. Lastly the catchment areas of the participating pediatric hospitals from which the set of controls was generated, reaches more than half of the childhood population in the country, compensating for issues associated with hospital controls.

In conclusion, this study provides support that over and beyond the already established inverse association of clinical allergic history with childhood ALL risk, a same magnitude inverse association also holds regarding an alternative measure, namely serologic markers of allergic predisposition, and serum IgE-reactivity, in particular. The reported results, however, do not seem to support the hypothesis that the reported parallel rising trends in both ALL and allergy during the last part of the 20th century might be on account of shared etiologic factors or a direct link between allergy and childhood ALL. Further epidemiological research is required to better understand possible associations between prior allergy and childhood ALL risk entailing appropriate study designs; to this end, prospectively collected allergy

information could minimize reporting biases, avail pretreatment biological indicators of allergic status, including total and specific levels of IgE and other relevant immune markers in order to avoid possible tumor- and treatment-related effects.

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Conflict of interest statement

None declared.

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