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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.

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