

Association of atopic diseases and parvovirus B19 with acute lymphoblastic leukemia in childhood and adolescence in the northeast of Brazil

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Abstract

Background Several factors related to the immune system, such as a history of allergies and virus infections, may be associated with acute lymphoblastic leukemia (ALL). The purpose of this study was to analyze whether the presence of atopic diseases and previous infection with parvovirus B19 and Epstein–Barr virus (EBV) are associated with the development of ALL.

Methods This case–control study was performed in two tertiary hospitals located in northeastern Brazil. The study population included 60 patients who were diagnosed with non-T-cell ALL using myelogram and immunophenotyping and 120 patients in the control group. Atopy was evaluated via a parent questionnaire and medical records. Total immunoglobulin (Ig)E and IgG levels of parvovirus B19 and EBV were measured in the serum. Logistic regression was performed to assess the association between variables and odds of ALL.

Results We identified a significant inverse association between rhinitis, urticaria and elevated IgE serum levels with ALL. A history of parvovirus B19 infection showed a significant association with this type of cancer [OR (95 % CI) 2.00 (1.94–4.26); $P = 0.050$]. In logistic regression, the

presence of atopy was a protective factor [OR (95 % CI) 0.57 (0.38–0.83); $P = 0.004$], and the presence of IgG for parvovirus B19 was an important risk factor for ALL [OR (95 % CI) 2.20 (1.02–4.76); $P = 0.043$].

Conclusions These results suggest that atopic diseases and elevated total IgE levels are associated with a potential protective effect on the development of ALL. Previous infection with parvovirus B19 contributed to ALL susceptibility.

Keywords Acute lymphoblastic leukemia · Atopic disease · Epstein–Barr virus · IgE-mediated allergy · Parvovirus B19 with ALL · Pediatrics

Abbreviations

ALL Acute lymphoblastic leukemia
EBV Epstein–Barr virus
OR Odds ratio

Introduction

Acute lymphoblastic leukemia (ALL) is defined as the abnormal, monoclonal and progressive proliferation of lymphoid precursors in the bone marrow with dissemination to the peripheral blood and infiltration to other organs, such as the nervous system, skin, testes, spleen and lymph nodes. This is the most common malignant neoplasia in children aged <15 years, accounting for 76–85 % of all leukemia diagnoses and representing >30 % of all malignant neoplasias in childhood [1, 2].

The etiology of ALL remains unknown, but the most important epidemiological modifier identified for the progression to childhood leukemia involves the development of the immune system [3]. The knowledge that exposure to infections might affect the etiology of leukemia

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in children resulted in three related hypotheses (Greaves, Kinlen, Smith). According to Greaves' hypothesis, ALL is caused by at least two mutations. Due to numerical or structural chromosomal alterations, preleukemic cell clones are formed in the first mutation, which occurs prenatally or shortly after birth. The second mutation may be enhanced by lower infection pressure early in life, which may result in abnormal immune responses [4, 5]. Kinlen's hypothesis involves population mixing and potential viral infection [6], and Smith's hypothesis specifically focuses on in utero infection as a potential cause of childhood leukemia. The latency period between the first epigenetic event and the emergence of the disease is relatively variable, ranging from a few months to many years [7].

There are few established risk factors for pediatric/adolescent leukemia, including predisposing genetic conditions and in utero or postnatal exposure to therapeutic irradiation or chemotherapeutic agents [8]. Atopic disease (i.e., asthma, eczema, rhinitis and urticaria) has been studied as a risk factor for several malignancies, including leukemia [9]. However, in a recent meta-analysis, Linabery et al. reported a consistent inverse association between a personal history of atopy/allergies, both overall and among individuals with asthma, eczema, hay fever (all investigated independently), and ALL in childhood [10].

Other potential agents involved in the development of ALL are viral infections. However, few data in the literature have shown an association between parvovirus B19 infection, Epstein–Barr virus (EBV) and leukemia in childhood and adolescence. These viruses have a tropism that is marked by human bone marrow, which replicates exclusively in erythroid progenitor cells [11].

The study objective was to evaluate the association between atopic diseases and a history of parvovirus B19 and EBV infection as potential factors that protect against or increase the risk of ALL, according to the clinical and laboratory data, among children and adolescents who live in northeastern Brazil.

Patients and methods

This hospital-based study was performed in two tertiary hospitals, the Oncology Center of the Oswaldo Cruz University Hospital in Recife–PE and Napoleão Laureano Hospital in João Pessoa–PB, from July 2011 to December 2013. It was a case–control study, consisting of 180 children and adolescents from Pernambuco and Paraíba, which are states in the northeast of Brazil. The participants were selected from patients who were diagnosed with ALL (cases) and among those who were not (controls), who were also treated at the same hospital of origin and living in the same geographic area.

To participate in this study, written permission was obtained from parents and caregivers. Research for this study was approved by the Ethics Committee of Human Research at the Federal University of Paraíba, Brazil (Reference Code: 0088.0.126.172-09).

Inclusion criteria included aged from 1–19 years, recent diagnosis of non-T-cell ALL, and not started treatment for leukemia. Exclusion criteria included patients who had a conflicting diagnosis of non-T-cell ALL, received corticosteroids in immunosuppressive doses, had been transfused within the past 6 months, died before blood collection, had congenital immunodeficiency, had not undergone laboratory tests that were standardized using the same technique, did not consent to undergo examinations, and had incomplete clinical historic data recounted by their parents or caregivers.

The patients who participated in this study consisted of 60 children and adolescents who were diagnosed with non-T-cell ALL classified because they had previously undergone a bone marrow myelogram and immunophenotyping. Participants with leukemia were matched to controls of the same age and gender at a ratio of 1:2. The control subjects, who had no history of malignant neoplasm or possibility of illness, included 120 children and adolescents who were consulted in the general pediatric ambulatory of the same hospital for annual monitoring of growth and development. Structured forms were used to interview the parents and caregivers of the patients and medical records data, including detailed tests performed during the medical visits.

Data collection

We used the same type of questionnaire for cases and controls, which was an interview form that was generated in the same hospital of origin. To characterize the allergies, the presence of a previous history of asthma was established through the use of medical records and clinical diagnosis, according to the following global initiative for asthma (GINA) recommendations [12]. The diagnosis was confirmed by the identification of reversible airflow limitations using pulmonary function test results by spirometry. Similarly, a history of allergic rhinitis was characterized via signs/symptoms (nasal congestion, rhinorrhea, sneezing, nasal itching, or pharyngeal itching and ocular itching), according to the allergic rhinitis and its impact on asthma (ARIA) initiative [13].

A history of atopic dermatitis was characterized according to diagnostic criteria defined in the Clinical Validation and Guidelines for the SCORAD Index, the Consensus Report of the European Task Force on Atopic Dermatitis, as described by Kunz and Oranje et al., which positively determined whether dermatitis was present and whether there was current exacerbation [14]. Finally, the urticaria

history was clinically characterized via questions that were designed according to the definition, classification and diagnosis of urticaria guidelines EAACI–European Academy of Allergy and Clinical Immunology; GA²LEN–Global Allergy and Asthma European Network; EDF–European Dermatology Forum; and WAO–World Allergy Organization [15–17]. The presence of urticaria at any stage of life may be acute (<6 weeks) or chronic (≥6 weeks).

Laboratory data

All 180 patients underwent individual clinical examinations and the collection of blood samples for laboratory tests. Blood samples were collected at initial diagnosis of leukemia in the case group. For the control group, blood samples were collected after 7–14 days of the medical appointment. Laboratory analysis of the serum levels of immunoglobulin type E (IgE) were measured using the IMMULITE[®] 2000 test kit, which is a solid phase, chemiluminescent immuno-metric assay (L2KIE6; Siemens, München, Germany). Values <60 UI/mL were considered normal for aged 1–5 years, <90 UI/mL for aged 6–9 years, up to 200 UI/mL for aged 10–15 years, and >200 UI/mL for aged >15 years, according to the reference values provided by the manufacturer.

Serum samples were obtained for the detection of parvovirus B19-specific IgM and IgG antibodies using enzyme-linked immunosorbent assay (ELISA-R; Biopharm AG, Darmstadt, Germany). IgG positivity was considered representative of remote infection, and IgM was considered indicative of a recent infection. Similarly, serum samples were obtained for the detection of antibodies (IgG) against the Epstein–Barr viral capsid antigen (VCA) in all cases and controls. Because basic sanitation problems are common in the northeast region of Brazil, parasitoids and helminthiasis may increase IgE levels, and thus the study patients absorbed a single 400 mg/dose of albendazole 2 weeks prior to blood collection.

Statistical analysis

The results are presented in table form with the absolute and relative frequencies. For the final study population of cases and controls, we compared the categorical variable (gender) using the chi-squared test and numerical variable (age) using Student's *t* test. To generate the model, $P \leq 0.05$ in the analysis represented significance. The potential associated risk or protective factors for ALL were assessed using logistic regression analysis. Multivariate analysis was performed to examine the multivariate-adjusted odds ratio (OR) for potential factors, such as asthma, rhinitis, urticaria, dermatitis, EBV (VCA) IgG, parvovirus B19 and total IgE serum. All tests were performed with 95 % confidence interval (CI). Logistic regression between the

variables studied and ALL was obtained according to gender, age, atopy, parvovirus B19 and EBV (VCA) IgG. The software STATA/SE 12.0 and Excel 2010 were used in the statistical analyses.

Results

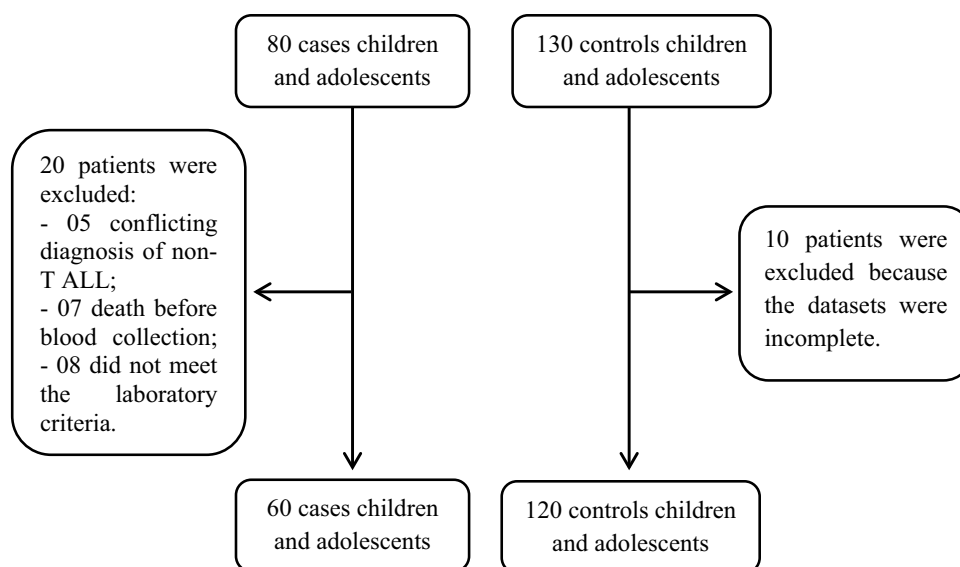
Eighty potential ALL cases were identified; however, 20 patients were excluded based on the following criteria—conflicting diagnosis of non-T-cell ALL (5/20), death before blood collection (7/20), and patients who did not meet the laboratory criteria (8/20). In the control group, 130 potential patients were originally identified; however, 10 patients were eliminated because their datasets were incomplete. The case group consisted of 60 patients with a confirmed diagnosis of non-T-cell ALL, and the control group consisted of 120 healthy patients who were treated in two tertiary hospitals (Fig. 1). No difference was observed between the genders in both groups, with a slight predominance of males. Close to 50 % of children in both groups were aged 1–6 years. Table 1 shows no significant differences between cases and controls.

Variables that were analyzed as risk or protective factors for ALL with a P value ≤ 0.05 are shown in Table 2. There was no significant difference between cases and controls for variables, such as asthma, dermatitis and EBV (VCA) IgG. Variables, such as rhinitis (31.7 % controls vs 16.7 % cases), urticaria (19.2 % controls vs 5.0 % cases) and elevated total IgE (51.7 % controls vs 13.3 % cases) were considered protective factors for ALL. In particular, the presence of parvovirus B19 IgG (20.0 % controls vs 33.3 % cases) was indicated [OR (95 % CI) 2.00 (1.94–4.26); $P = 0.050$] as a risk factor for ALL. The tests did not detect the presence of IgM to parvovirus B19 in either group.

In a logistic regression of the variables analyzed, the presence of atopy, which was potentially represented by rhinitis and urticaria, showed a protection factor for ALL [OR (95 % CI) 0.57 (0.38–0.83); $P = 0.004$], and the presence of parvovirus B19 IgG was a risk factor [OR (95 % CI) 2.20 (1.02–4.76); $P = 0.043$], as shown in Table 3.

Discussion

In this hospital-based case–control study, we investigated the variables that may be associated with ALL. We found that rhinitis, urticaria and elevated IgE levels demonstrated in the control group were associated as protective factors for ALL. Regarding infectious causes, the presence of parvovirus B19 IgG in greater frequency in the case group was considered a risk factor for ALL.

Fig. 1 Flowchart of the study population**Table 1** Demographic profile of the study population

Variables	Groups		Odds (IC)	P value
	Cases	Controls		
	N (%)	N (%)		
Gender				
Male	34 (56.7)	64 (53.3)	1.14 (0.59–2.24)	0.791 ^a
Female	26 (43.3)	56 (46.7)	1.00	
Age				
1–6 years	29 (48.4)	59 (49.2)	0.98 (0.42–2.31)	0.992 ^b
7–11 years	17 (28.3)	33 (27.5)	1.03 (0.40–2.69)	
12–18 years	14 (23.3)	28 (23.3)	1.00	

^a Chi-squared test^b Student's *t* test

This raises the question of whether there is a relationship between ALL in children and a preceding history of allergy, as observed by Hughes and Lightfoot et al. Studies from the United Kingdom Childhood Cancer Study (UKCCS) analyzed this topic; in 2007 [18], one study had already related preceding asthma history, rhinitis and atopic dermatitis with ALL risk. There was a 30 % risk reduction for acute lymphoid leukemia in patients with a history of atopic dermatitis, with an OR of 0.70 (0.51–0.97; 95 % CI). A stronger association was found for patients who had allergic rhinitis with an OR of 0.47 (0.26–0.85; 95 % CI). These findings strongly suggest that there was an inverse relationship between a history of allergy and ALL in children, which is consistent with the hypothesis that an unregulated immune response would have a close association with ALL in childhood.

Table 2 Odds ratios for acute lymphoid leukemia risk with numerous variables on a sample of 60 cases and 120 controls

Variables	Groups		Odds (IC)	<i>P</i> value ^a
	Cases	Controls		
	<i>N</i> (%)	<i>N</i> (%)		
Asthma				
Positive	11 (18.3)	34 (28.3)	1.00	0.201
Negative	49 (81.7)	86 (71.7)	1.76 (0.77–4.07)	
Rhinitis				
Positive	10 (16.7)	38 (31.7)	1.00	0.049
Negative	50 (83.3)	82 (68.3)	2.32 (1.00–5.46)	
Urticaria				
Positive	3 (5.0)	23 (19.2)	1.00	0.020
Negative	57 (95.0)	97 (80.8)	4.51 (1.21–19.77)	
Dermatitis				
Positive	3 (5.0)	13 (10.8)	1.00	0.308
Negative	57 (95.0)	107 (89.2)	2.31 (0.58–10.67)	
EBV (VCA) IgG ^b				
Reactive	34 (56.7)	60 (50.0)	1.00	0.493
Non-reactive	26 (43.3)	60 (50.0)	0.76 (0.39–1.49)	
Parvovirus IgG				
Reactive	20 (33.3)	24 (20.0)	2.00 (1.94–4.26)	0.050
Non-reactive	40 (66.7)	96 (80.0)	1.00	
IgE total				
Elevated	8 (13.3)	62 (51.7)	1.00	<0.001
Normal	52 (86.7)	58 (48.3)	6.95 (2.87–17.37)	

^a Chi-squared test^b EBV (VCA) IgG: Epstein–Barr–IgG viral capsid antigen

Another investigation, which preceded the UKCCS, also supported this hypothesis. In relationship to this study, the difference was that their study was a hospital-based

Table 3 Logistic regression between the variables studied and acute lymphoid leukemia

Variables	Odds ratio	P value	95 % CI
Sex	1.11	0.737	(0.58–2.15)
Age	0.96	0.403	(0.89–1.04)
Atopy	0.57	0.004	(0.38–0.83)
Parvovirus B19 IgG	2.20	0.043	(1.02–4.76)
EBV (VCA) IgG ^a	1.68	0.128	(0.23–1.21)

^a EBV (VCA) IgG: Epstein–Barr–IgG viral capsid antigen

case–control study performed by Linet and McCaffrey et al. in 1986, in which rhinitis, atopic eczema, asthma and urticaria were analyzed as risk factors, and there was a high inverse association for rhinitis, dermatitis and urticaria [19]. In 2010, a meta-analysis study performed by Linabery and Jurek et al. summarized the epidemiological evidence of an association between ALL and allergy in published studies from 1952–2009 [20]. That report included 10 case–control studies, eight of which reported an inverse association between allergy and ALL. The relationship between ALL and asthma presented with an OR of 0.79 (0.61–1.02; 95 % CI), which was 0.74 (0.58–0.96) for eczema, and 0.55 (0.46–0.66) for allergic rhinitis. In 2011, a study by Chang et al. utilized the National Health Insurance Research Database of Taiwan and reported a result that completely differed from most research related to the subject. The study utilized a population-based case–control design and observed a positive relationship in the association between allergies and ALL [21]. Consequently, the prevalence of allergic diseases in patients with ALL did not indicate that an allergic disease was a protective factor. Furthermore, this research included biases that may have affected the results.

In 2012, Linabery and Spector, in an invited commentary, emphasized both the importance of biases in research and the current uncertainty in the direction of the relationship between allergies and ALL [10]. Indeed, it is possible that a patient diagnosed with allergic disease has immune hyperactivity, which can serve as an alert and help prevent ALL, a potentially lethal disease. Thus, it is possible that facing numerous environmental stresses from the modern world, such as allergy symptoms, may protect the body from subtle epigenetic changes and lymphocyte clones. Thus, we could have an expansion of the hygiene hypothesis in which the absence of infectious processes, despite the induction of a Th2 immune deviation towards IgE overproduction and atopic diseases, protects against the development of ALL. The exacerbated response of the immune system in allergic diseases may keep the immune system free from ALL.

The immune surveillance hypothesis states that the immune system recognizes antigens of malignant cells

as foreign and generates a response to these stimuli, preventing the development of many cancers, as observed by Markiewicz and Gajewski [22]. The presence of an atopic condition would increase the immune system surveillance by monitoring, identifying and eliminating malignant cells, as observed by Turner et al. [9]. In support of this hypothesis, Kersey and Shapiro et al. observed that immunocompromised people have a high risk of developing non-Hodgkin lymphoma, a malignancy with a histology that is identical to acute lymphoid leukemia [23].

The precise underlying human biology has not been established, but there is evidence supporting antitumor immunity mediated by CD4+ T-helper 2 (Th2) cells that are specific for a given tumor antigen. The release of Th2 cytokines recruits and activates eosinophils, macrophages, type 2 CD8+ T cells and natural killer cells, which participate in tumor surveillance and perform antitumor attacks. Th2 cytokines also have other important functions, including tumor necrosis factor- α directing antitumor cytotoxic effects, interleukin-4 (IL-4) inhibiting angiogenesis, and IL-10 reducing the expression of inflammatory cytokines and directly inhibiting any type of inflammation associated with carcinogenesis [24].

In 2001, Kinlen reported that the growing number of cases of leukemia in specific population groups, is most likely due to population mobility and mixture, resulting in the onset of new infectious agents in subjects who were previously unexposed or susceptible, triggering immunological events and causing transformations after infections [25]. The presence of an infection would induce a cellular immune response that is mediated by T-lymphocytes. In this context, abnormal responses to infections could result in leukemia, via the abnormal proliferation of immune cells or a failure to contain the malignant expansion of the abnormal immune system [26]. Parvovirus B19 belongs to the *Parvoviridae* family, which has genetic material on a single DNA strand and presents with tropism in erythroid progenitor cells that are derived from bone marrow bone and blood; in these cells, it replicates and inhibits erythropoiesis, causing cytotoxic effects. The infection starts when the capsid binds to P antigens (one glycosphingolipid) and the red blood cell line (specifically, the pro-erythroblasts), taking advantage of the active division of these cells to replicate [27]. A potential mechanism whereby a viral infection can affect the process of leukemogenesis is via altering DNA methylation, changing the expression of hematopoietic genes, which may persist after viral elimination. The cell's response to the viral infection may result in the activation of new DNA methylation processes in its effort to control viral gene expression [26]. Exposure to a variety of antigens may be protective throughout the normal modulation and development of the immune system, and a strong reaction to infectious agents may induce widespread

immune stimulation as well as specific anti-viral defenses that may affect leukemogenesis, particularly for a virus, such as parvovirus B19, which has bone marrow tropism [27, 28].

However, our study had some limitations. First, there was recall bias of signs and symptoms suggestive of asthma, rhinitis, dermatitis and remote viral infections between case and control patients, but these were minimized by medical records and tests performed during the medical appointment. The presence of EBV (VCA) and parvovirus B19 IgG reflects remote infection, which is not necessarily dependent on the parents and caregivers to obtain previous information of infections by these viruses. Second, selection bias was minimized by the choice of incident cases that had not yet started treatment for ALL and the control patients who were undergoing a routine visit at the pediatric clinic of the same hospital. Third, confounding bias could be minimized by identifying a control group, which did not have ALL but demonstrated an age and gender similarity to the case group. Analytical techniques were performed to reduce the possibility of confounding factors.

Our research provided evidence that there was an inverse association between urticaria, rhinitis, and elevated IgE levels and ALL; however, remote infection with parvovirus B19, confirmed by measurement of IgG levels, was associated with ALL and contributed to the susceptibility of this cancer in children and adolescents in northeastern Brazil.

Despite the use of an epidemiological approach, the characterization of exposure in cases and controls was performed more precisely by clinical examination and laboratory data of the researched patients. The study results are clinically and epidemiologically relevant; however, our findings also require further validation in larger, preferably population-based studies, including different populations, such that epigenetic variations can be discovered and the ALL etiology in pediatric patients can be better elucidated.

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Compliances with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Participating hospitals Oncology Center of the Oswaldo Cruz University Hospital in Recife–PE, Brasil and Napoleão Laureano Hospital in João Pessoa–PB, Brasil.

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