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# Allergy and acute leukaemia in children with Down syndrome: a population study. Report from the Mexican inter-institutional group for the identification of the causes of childhood leukaemia

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**Background:** Allergies have been described as protective factors against the development of childhood acute leukaemia (AL). Our objective was to investigate the associations between allergy history and the development of AL and acute lymphoblastic leukaemia (ALL) in children with Down syndrome (DS).

**Methods:** A case-control study was performed in Mexico City. The cases ( $n=97$ ) were diagnosed at nine public hospitals, and the controls ( $n=222$ ) were recruited at institutions for children with DS. Odds ratios (OR) were calculated.

**Results:** Asthma was positively associated with AL development (OR = 4.18; 95% confidence interval (CI): 1.47–11.87), whereas skin allergies were negatively associated (OR = 0.42; 95% CI: 0.20–0.91).

**Conclusion:** Our findings suggest that allergies and AL in children with DS share biological and immune mechanisms. To our knowledge, this is the first study reporting associations between allergies and AL in children with DS.

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Acute leukaemia (AL) is the most common childhood cancer worldwide. Mexico City has one of the highest rates of AL at 57.6 cases per million; acute lymphoblastic leukaemia (ALL) is the most common subtype (85.1%; Pérez-Saldivar *et al*, 2011).

Down syndrome (DS) is one of the most important childhood leukaemia-predisposing syndromes (Xavier and Taub, 2010). Children with DS have a 10- to 20-fold higher risk of developing AL compared with children without DS (Ross *et al*, 2005). The mechanism behind this increased susceptibility is not thoroughly known; however, it may be explained by the gene dosage effect caused by the additional copy of chromosome 21, which could be involved in the malignant transformation of haematopoietic cells (Xavier and Taub, 2010). Mutations in several genes on chromosome 21 have been identified in leukaemia, and many of these genes have been recognised as encoding transcription factors that act at various stages of haematopoiesis. In addition, trisomy 21 contributes to the development of *GATA1* mutations, which are involved in leukaemogenesis, particularly in acute megakaryoblastic leukaemia (Look, 2002; Malinge *et al*, 2009). In addition, it has been suggested that trisomy 21 increases the proliferation of normal lymphoid progenitors; however, it must be accompanied by other events, such as exposure to environmental factors, that could potentially cause leukaemia in DS children (Levanon *et al*, 2001; Mejía-Aranguré *et al*, 2003; Valladares *et al*, 2005; Mejía-Aranguré *et al*, 2007; Rabson, 2010). Moreover, it has been proposed that allergies influence the development of childhood leukaemia. Different studies have been conducted in this field; however, their results are not conclusive, as different studies have concluded that allergies are risk or protective factors (Schüz *et al*, 2003; Spector *et al*, 2004; Rosenbaum *et al*, 2005; Söderberg *et al*, 2006; Hughes *et al*, 2007; Rudant *et al*, 2010; Chang *et al*, 2012). In addition, the mechanisms involved in the relationship between allergies and leukaemia are not completely understood.

Various immunological disorders have been described in children with DS (Kusters *et al*, 2009) that, along with these children's high susceptibility to AL, would provide additional evidence in the relationship between allergies and the development of AL.

The present study was conducted by the Mexican Inter-Institutional Group for the Identification of the Causes of Childhood Leukaemia (MIGICCL). To our knowledge, this is the first study to evaluate the association between allergies and AL in DS children.

## MATERIALS AND METHODS

The study has been described in greater detail elsewhere (Flores-Lujano *et al*, 2009) and is described briefly below. This case-control study was performed by the MIGICCL. The cases were DS patients diagnosed with AL and younger than 19 years old ( $n = 97$ ). The diagnosis of AL was established by bone marrow aspirates and karyotype studies. The cases were recruited during two periods; the first corresponded to 1998–2005, when six public institutions in Mexico City participated under the auspices of the Instituto Mexicano de Seguro Social (IMSS), Instituto de Seguridad Social al Servicio de los Trabajadores del Estado and Secretaría de Salud. The second period was from 2006 to 2011 and incorporated three additional institutions. It is estimated that 97.5% of children with AL in Mexico City have attended at these public health institutions (Pérez-Saldivar *et al*, 2011). The control group consisted of children with DS children who were younger than 19 years old and did not have AL ( $n = 222$ ). The controls were not matched with the cases according to other variables. At the time of the study, DS children residing in Mexico City could only be enrolled in two types of institutions (Centres of Multiple Attention and Specialized Centres), which offer specialised education to

individuals with DS. There were 76 CMAs; however, children with DS from these institutions were not included in the present research because karyotype study was not part of the admission requirements. The specialised centres did require a karyotype study before children with DS were admitted; only three of the five specialised centres were selected because of logistic issues. From these centres, 78% of children with DS who were younger than 19 years were included in the present study; if any of the control children developed AL medical care was provided by one of the hospitals that served as sources of the cases. Down syndrome children with transient megakaryoblastic leukaemia and/or AML that developed after the resolution of transient neonatal leukaemia were not excluded from this study. The children's parents were interviewed by a trained nurse. Before the information was collected, an informed consent was obtained from the parents. After data were collected, they were compiled using a previously standardised questionnaire (Flores-Lujano *et al*, 2009). Each child's medical history (allergies, infections during the first year of life, cardiopathies, and hospitalisations) was explored. The cases' parents were required to indicate whether their children had allergies for at least 1 year before the diagnosis of AL, whereas the control children's parents were asked about the occurrence of allergies at least 1 year before the interview. The parents were questioned about the specific type of allergy (asthma, rhinitis, skin allergy, and other allergies), emphasising the difference between allergy and infectious diseases. It is worth noting that the specific dates of diagnosis and symptoms of the allergic diseases were not explored in the present research. Stacking level was used as a proxy for socioeconomic status and was estimated by the number of people per room in a household and classified according to the criteria of Bronfman *et al* (1988): not crowded, up to 1.5 people per room; semi-crowded and crowded, >1.6 people per room. For the analysis, the last two categories were classified as a low stacking level.

**Statistical analysis.** Analyses were performed using SPSS IBM (Statistical Package for the Social Sciences, Inc., Version 21, Chicago, IL, USA). Each independent variable (skin allergy, rhinitis, bronchial asthma, and other allergies) was stratified for the control variables to control confounding factors that may alter the effect of independent variables. The covariates were dichotomised for statistical purposes. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for all independent variables and for DS children with and without ALL in unconditional logistic regression models. The variables included in the initial logistic regression models were as follows: gender, birth weight, birth order, breastfeeding, age at leukaemia diagnosis, infection during the first year of life, cardiopathies, stacking level, maternal information (age at child's birth, education, occupation, and smoking), and paternal information (education, occupation, and smoking). For the final logistic regression models, the variables infection during the first year of life, cardiopathies and paternal education were not included. Two interactions were identified during the statistical analyses (breastfeeding and age at leukaemia diagnosis); consequently, the studied population was divided by these variables.

## RESULTS

Acute lymphoblastic leukaemia was observed in 65% of the cases. Breastfeeding was equally common among the cases and the controls ( $P = 0.86$ ). Twenty-six per cent of the cases reported at least one allergic condition: asthma, rhinitis, skin allergy, or other allergies. The predominant type of allergy corresponded to the skin and was reported more frequently by controls than cases

( $P=0.026$ ). However, asthma was more frequently reported for cases than for controls ( $P=0.004$ ; Table 1).

Asthma was positively associated with AL development (OR=4.18; 95% CI: 1.47–11.87), whereas skin allergy was negatively associated with AL (OR=0.42; 95% CI: 0.20 to –0.91). Asthma persisted as a risk factor for children with ALL; when the children were divided by whether they were breastfed (yes/no), the results were not statistically significant (Tables 2 and 3). After stratification by age at diagnosis, the result of this variable was similar (Supplementary Data). The protective effect observed for skin allergy was notable in children with AL and ALL who were not breastfed (Table 3). The same trend was observed for this variable after stratification by age at diagnosis, but statistical significance was not observed. Significant associations were not observed for rhinitis and other allergies in children with AL and ALL (Table 3 and Supplementary Table).

**DISCUSSION**

The results of the present study suggest that asthma is a risk factor for AL in children with DS, whereas skin allergies seemed to protect the population from AL. Children with DS are more vulnerable to the effects of environmental factors that have been associated with the development of AL (Mejía-Aranguré *et al*, 2003, 2007). In addition, our previous study found that early infections that have been regarded as protective factors against the development of childhood AL in the general population were risk factors for children with DS (Flores-Lujano *et al*, 2009). Thus, the intrinsic immune dysregulation that is well described in children with DS (Kusters *et al*, 2009) likely has a significant role in the association between allergic phenomena and AL.

The positive associations observed between asthma and ALL were similar to the findings of a study conducted in the western United States (Spector *et al*, 2004) and another conducted in Taiwan (Chang *et al*, 2012). However, other authors have reported negative associations (Schüz *et al*, 2003; Rosenbaum *et al*, 2005; Söderberg *et al*, 2006; Hughes *et al*, 2007; Rudant *et al*, 2010), as have two meta-analyses (Dahl *et al*, 2009; Linabery *et al*, 2010). Spector *et al* (2004) and Chang *et al* (2012) argued that the discrepancies between their results and those of other authors were caused by exposure data. The authors of these two studies obtained information from medical records, which are supposedly free of parental recall bias; whereas other authors and the present study administered questionnaires to the children’s parents. It is important to highlight that one of the major advantages of using questionnaires in research is that they allow researchers to measure various and different variables using a single tool.

Furthermore, negative associations were observed between skin allergy and AL, and this trend remained when the group was divided according to the presence of ALL. This negative association is consistent with the findings of other studies (Schüz *et al*, 2003; Rosenbaum *et al*, 2005; Hughes *et al*, 2007; Rudant *et al*, 2010) and meta-analyses (Dahl *et al*, 2009; Linabery *et al*, 2010).

However, Spector *et al* (2004) and Chang *et al* (2012) showed contradictory results, for example, that a history of atopy or hives was positively associated with ALL. One factor that may have contributed to these differing results was the age of the studied population. Spector *et al* (2004) investigated children younger than 6 years old, and Chang *et al* (2012) included children between 1 and 10 years old; both of these study populations were younger than those of other studies. Another factor was the different definitions of skin manifestations of atopy.

In addition, in two recent reviews (Chang *et al*, 2009; Linabery *et al*, 2010), the authors have reported an inverse association

**Table 1. Sample characteristics of children with Down syndrome and acute leukaemia from Mexico City**

Variables	Cases (n = 97)		Controls (n = 222)		OR (CI 95%)
	n	%	n	%	
<b>Gender</b>					
Female	52	53.6	102	45.9	
Male	45	46.4	120	54.1	
Weight at birth (>2600 g)	60	62.5	112	51.4	0.63 (0.38–1.03)
Firstborn child	22	22.7	74	33.3	0.58 (0.33–1.01)
Breastfed	63	64.9	142	64	1.04 (0.63–1.71)
Age > 6 years <sup>a</sup>	46	47.4	128	57.7	0.66 (0.41–1.07)
Stacking	58	59.8	76	34.2	2.85 (1.74–4.67)
Infection during the first year of life	24	24.7	57	25.7	0.95 (0.54–1.65)
Cardiopathies	13	13.4	68	30.6	0.35 (0.18–0.67)
<b>Allergy history</b>					
Bronchial asthma	10	10.3	6	2.7	4.18 (1.47–11.87)
Rhinitis	6	6.2	19	8.5	0.69 (0.26–1.78)
Skin allergy	9	9.3	43	19.4	0.42 (0.20–0.91)
Other allergies	12	12.4	27	12.2	1.03 (0.49–2.13)
Overall allergies	25	25.8	73	32.9	0.69 (0.40–1.17)

Abbreviations: CI = confidence interval; OR = odds ratio.  
<sup>a</sup>Age > 6 years: age at leukaemia diagnosis for cases or age at interview for controls.

**Table 2. Logistic regression model for allergy history in children with DS**

Variables	Children with AL		Children with ALL	
	OR	CI 95%	OR	CI 95%
Skin allergy	0.42	0.18–0.97	0.26	0.08–0.83
Rhinitis	1.07	0.34–3.32	1.01	0.24–4.20
Bronchial asthma	3.29	0.97–11.14	4.24	1.01–17.79
Other allergic diseases	1.56	0.65–3.75	1.84	0.71–4.72
Overall allergies	0.75	0.39–1.42	0.83	0.39–1.75

Abbreviations: AL = acute leukaemia; ALL = acute lymphoblastic leukaemia; CI = confidence interval; DS = Down syndrome; OR = odds ratio. Odds ratios were adjusted for the following variables: gender, weight at birth, birth order, breastfeeding, age at diagnosis of leukaemia, stacking level, maternal information (age at child’s birth, education, occupation, and smoking), and paternal information (occupation and smoking).

between allergies and childhood AL. It has been argued that very few studies have researched this relationship and their results must be interpreted in the light of certain limitations, such as exposure data and latency period, which affect study results (Linabery *et al*, 2010).

Moreover, the opposite results observed in the present research suggest that asthma is a risk factor for the development of AL in DS children, whereas skin allergy is a protective factor. One possible explanation for our observations is the radiological studies and treatments that were administered to the children; however, these variables were not explored in the present study.

In the present study, exposures were assessed only via interview; it is possible that asthma was misclassified, as it can

Table 3. Logistic regression model for allergy history in children with DS by breastfeeding and ALL

Variables	Children with AL Breastfeeding				Children with ALL Breastfeeding			
	Yes		No		Yes		No	
	OR	CI 95%	OR	CI 95%	OR	CI 95%	OR	CI 95%
Skin allergy	1.22	0.26–5.67	0.20	0.06–0.70	1.21	0.22–6.62	0.06	0.01–0.60
Rhinitis	16.47	1.29–209.13	0.42	0.08–2.04	16.45	0.85–316.11	0.25	0.02–2.76
Bronchial asthma	2.47	0.39–15.74	2.75	0.47–15.90	2.05	0.21–20.03	5.64	0.71–44.76
Other allergic diseases	1.00	0.14–7.12	1.94	0.66–5.67	1.69	0.26–10.83	2.51	0.71–8.85
Overall allergies	0.98	0.27–3.47	0.63	0.28–1.44	1.08	0.27–4.20	0.77	0.29–2.08

Abbreviations: AL = acute leukaemia; ALL = acute lymphoblastic leukaemia; CI = confidence interval; DS = Down syndrome; OR = odds ratio. Odds ratios were adjusted for the following variables: gender, weight at birth, birth order, age at leukaemia diagnosis, stacking level, maternal information (age at child's birth, education, occupation, and smoking), and paternal information (occupation and smoking).

be confounded with other respiratory infections, resulting in over-reporting by parents. The frequencies of wheezing and asthma in general population are ~36.1% and 55.5%, respectively, (Wright, 2002). In children with DS, however, the frequency of wheezing has been reported as between 18.5 and 36%, and the reported frequency of asthma is between 3.1 and 19.4% (Munoz-Lopez, 2011; Weijerman *et al*, 2011). It is worth noting that these frequencies were determined via questionnaire. In the present investigation, the frequency of asthma was 2.7% and 10.4% for controls and cases, respectively; therefore, the frequency observed for asthma in this study was not higher than that reported in the studies mentioned, and the possibility of over-report is low.

The reported frequency of skin allergy in children with DS is between 9.2 and 15.4% (Munoz-Lopez, 2011; Weijerman *et al*, 2011). In the present study, the frequency was 9.4% and 19.5% for cases and controls, respectively; thus, the frequencies determined in this study were similar to those previously reported.

It is worth noting that in the present study, the same questionnaire was used for cases and controls; if the parents made mistakes when remembering the details of an asthma or skin allergy diagnosis, the mistakes were equally likely for both groups. This would provoke a non-differential misclassification bias with a possible underestimation of the association, and the associations found would be higher. Moreover, we cannot presume that cases' parents over-reported asthma and under-reported skin allergy; if asthma was confounded with respiratory infections and/or cardiopathies, both would have behaved as confounding factors or interaction variables in the analysis, which was not the case. In the stratified analysis, when the infections during the first year of life were taken into account, the trend of asthma and skin allergy remained positively and negatively associated with AL, respectively, ( $P = 0.616$  and  $P = 0.289$ , respectively;  $P$  values of the  $\chi^2$  test for heterogeneity). In addition, a similar trend was observed when cardiopathies were included in the stratified analysis ( $P = 0.738$  and  $P = 0.214$ , respectively;  $P$  values of the  $\chi^2$  test for heterogeneity). The possibility of a selection bias in the present study was low because it is estimated that 97.5% of children with AL in Mexico City attend the nine public institutions that participated in this research (Pérez-Saldivar *et al*, 2011). Regarding the controls, 78% of the population younger than 19 years old from the three participating centres was included in the research (Flores-Lujano *et al*, 2009). All of the parents of cases and controls answered the questionnaire.

The association between allergies and AL in children suggests common biological mechanisms, which have been described in the context of two hypotheses: the antigenic stimulation hypothesis and the immunosurveillance hypothesis (Söderberg *et al*, 2004). To explain the role of allergies as a risk factor for cancer, is worth considering the antigenic stimulation hypothesis, which proposes that the chronic stimulation of the immune system will provoke randomly occurring pro-oncogenic mutations in actively dividing cells (Söderberg *et al*, 2004). In comparison, allergies as protective factors can be explained in terms of the immune-surveillance hypothesis, which suggest that allergic diseases enhance the immune system's ability to detect and eliminate neoplastic cells (Söderberg *et al*, 2004). We suggest that another possible hypothesis is the adrenal hypothesis (Schmiegelow *et al*, 2008), which proposes that infections produce changes in the hypothalamus-pituitary-adrenal axis and subsequently an elevation in plasmatic cortisol, provoking the elimination of leukaemic and preleukaemic cells. This mechanism would be possible in allergic conditions because the drugs commonly used to treat allergies include corticosteroids (Allergy UK British Allergy Foundation, 2012), which could provide the same protective effect against the development of AL that early infections provide.

In contrast, it has been reported that children with wheezing caused by common viral infections (rhinovirus and respiratory syncytial virus (RSV)) are at increased risk of developing asthma (Boyce *et al*, 2009). In addition, the predisposition to these infections is determined by interactions with some genes (Çalışkan *et al*, 2013). Children with DS have genetic characteristics that make them more susceptible to infections, including those caused by RSV (Bloemers *et al*, 2010; Weijerman *et al*, 2011; Zachariah *et al*, 2012). Therefore, DS children exposed to these viruses may be at increased risk of developing asthma and subsequently, according to the results of the present study, for developing AL. However, this hypothesis requires further research to elucidate the relationship between genetic susceptibility to the development of RSV infections that in turn increase the risk of asthma and possibly AL in children with DS.

The major strength of the present research is that it is the first to report associations between allergies and AL in children with DS, a population highly susceptible to AL. Our results suggest that asthma is risk factor for AL in children with DS, whereas skin allergy appeared to be protective factor. These results must be interpreted in the light of some limitations. Although the most relevant results in the present study were consistent with previous

research, future studies are required to elucidate the association between allergies and AL in children with DS.

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