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Pediatric Acute Lymphoblastic Leukemia and Exposure to Pesticides

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Abstract

Organophosphates are pesticides ubiquitous in the environment and have been hypothesized as one of the risk factors for acute lymphoblastic leukemia (ALL). In this study, we evaluated the associations of pesticide exposure in a residential environment with the risk for pediatric ALL. This is a case–control study of children newly diagnosed with ALL, and their mothers (n = 41 child–mother pairs) were recruited from Georgetown University Medical Center and Children's National Medical Center in Washington, DC, between January 2005 and January 2008. Cases and controls were matched for age, sex, and county of residence. Environmental exposures were determined by questionnaire and by urinalysis of pesticide metabolites using isotope dilution gas chromatography–high-resolution mass spectrometry. We found that more case mothers (33%) than controls (14%) reported using insecticides in the home ($P < 0.02$). Other environmental exposures to toxic substances were not significantly associated with the risk of ALL. Pesticide levels were higher in cases than in controls ($P < 0.05$). Statistically significant differences were found between

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children with ALL and controls for the organophosphate metabolites diethylthiophosphate ($P < 0.03$) and diethyldithiophosphate ($P < 0.05$). The association of ALL risk with pesticide exposure merits further studies to confirm the association.

Keywords

organophosphates; insecticides; childhood cancer; clinical toxicology; ALL

Introduction

Childhood leukemia represents 31% of all cancers occurring among children aged 15 years and younger and has an annual incidence rate of 43 cases per million in the United States.[1,2] Acute lymphoblastic leukemia (ALL) is the most common type of all childhood cancers, with most of the cases occurring between the ages 3–7 years.[1,2]

Little is known about the risk factors for childhood ALL; children with Down syndrome have a 10- to 20-fold increased risk of leukemia.[3,4] Exposure to diagnostic x-rays in utero is another of the hypothesized causes of pediatric ALL.[5,6] The evidence points to low-level irradiation of the fetus associated with an increasing risk of leukemia in childhood. In contrast to exposure in utero, there are conflicting data from case–control studies for an association between childhood leukemia and postnatal exposure to medical diagnostic irradiation.[5] Moreover, because an extremely low number of individuals are exposed, the population attributable risk is quite small.[7] Electromagnetic radiation exposure, maternal history of fetal loss, and high infant birth weight have also been suggested as possible risk factors for pediatric ALL, but the associations are inconsistent.[8] Another potential risk factor is chromosome translocations involved in the ALL pathway that may occur prenatally during fetal hematopoiesis and can initiate leukemogenesis, but these would require additional postnatal events to result in leukemia.[9] Thus, maternal genotoxic exposures might trigger nonhomologous chromosome rearrangement and can initiate malignancy if further exposed to chemical or infectious agents during early childhood.[10]

Organophosphates (OPs) are contemporary pesticides in commercial and consumer use and the most common class of insecticides used in homes and gardens. Chronic residential use and the heavy agricultural use of these chemicals on crops, fruits, and vegetables continually expose humans to pesticides via the food chain, air, and water supply. Therefore, children have a high potential to become exposed to pesticides through the diet and home environment.[11–17] Some studies have reported that OP concentrations were higher in young children than in adolescents and adults,[13,18] and pesticides detected in cord and newborn blood indicate that pregnant women and their fetuses are exposed to pesticides.[12,15,18–20] Recent evidence suggests that maternal exposure to pesticides may be associated with childhood ALL. Approximately 2-fold increase in risk associated with no-pest strips and home use of pesticides and inconsistent associations with professional extermination have been reported.[21–26]

The aim of this study is to investigate the association of household pesticide exposures with the risk of childhood ALL in the Washington, DC, metropolitan area.

Materials and Methods

This hospital-based case–control study focuses on biospecimen analysis and self-reported environmental exposure questionnaires of mothers and children. The purpose is to examine the association of pesticide exposures with an increased risk of ALL. The study was

approved by Georgetown University Medical Center (GUMC) and Children's National Medical Center Institutional Review Boards.

Case Eligibility

Children younger than 18 years, diagnosed within the previous 6 months with ALL, were eligible to participate in the study. Subjects with a diagnosis of Down syndrome or other chromosomal disorder, single-gene disorder, or recognized multiorgan syndrome were excluded. Only residents from the metropolitan Washington, DC, area were eligible to participate. When eligible children were identified, the parents were consented. Children older than 7 years were required to sign an assent form, and children older than 12 years were asked to sign an assent form designated for the 12–18 years of age category.

Selection of Controls

Controls were selected from the same general referral source population as the cases. Controls were recruited from outpatient pediatric clinics at GUMC and Children's National Medical Center. The control subjects were healthy children who attended the outpatient clinic for annual immunization, well visits, or some other minor ailment matched to the cases by sex, age at diagnosis (within 2 years), and place of residence (Maryland, the District of Columbia, or Virginia). Once recruited, the controls were consented and assented appropriately; children between the age of 7 and 12 signed an assent form especially designed for that age group, whereas children older than 12 signed an assent form designed for children between the ages of 12 and 18.

Questionnaire Data

An extensive environmental questionnaire was administered to all mothers. The questionnaire was specifically designed for this study by adapting other well-validated questionnaires such as those used by the Children's Oncology Group for studies of infant leukemia.[27,28] The items included on the questionnaire assessed sociodemographic variables, medical history, neighborhood and home characteristics, history of active and passive smoking, alcohol consumption, dietary and nutritional components, occupational and household exposures of parents during the period of preconception (6 months) and during pregnancy (9 months), and current behaviors and exposures. The history of pesticide exposures included type of pesticide, presence of pests and frequency in the home (ie, cockroaches, mice, rats, or other pests), other pest control measures, lawn services, and the use of pest control for pets. Interviews were conducted in person, by a trained interviewer, and some were completed over the telephone (<30%) by trained bilingual interviewers, either in Spanish or in English as appropriate. The study and the questionnaire were presented to the parents as a study of environmental factors associated with the period just before or during the pregnancy. Questions were focused on medical, nutritional, and chemical exposures in general, at home, at work, and at hobbies. Pesticides were never singled out as the focus of the study to prevent recall bias.

Biological Sampling

Samples were analyzed at The Centers for Disease Control and Prevention Toxicology Laboratory for pesticides and creatinine using sophisticated technology for biological specimen analysis. Samples collected from both mothers and children were stored at −80°C and shipped frozen in batches for analysis. The samples first underwent simple solid phase extraction, followed by a highly selective analysis using isotope dilution gas chromatography–high-resolution mass spectrometry.[18,29] The method has limits of detection in the low picogram per gram range and coefficients of variation of typically less than 10% at the low picogram per gram end of the method linear range. By using this method, OPs,

carbaryl/naphthalene, propoxur, bendiocarb, chlorpyrifos, diazinon, dicloran, captan, and folpet or their metabolites can be quantified in the general population.[30,31] Creatinine concentrations were determined using a commercially available diagnostic enzyme method (Vitros CREA slides). All batches tested included 10% quality control samples that were blinded as to case or control status or maternal or child status (Table 1).

Statistical Analysis

Statistical analysis was conducted by the Department of Biostatistics, Bioinformatics, and Biomathematics, Lombardi Comprehensive Cancer Center, GUMC. First, the data were examined for case–control differences using Cochran–Mantel– Haenszel test of marginal homogeneity, Wilcoxon signed rank sum test, and paired *t* test. The main effect of maternal pesticide exposure reported by questionnaire and measured from urine samples were examined using Fisher exact test, Pearson χ^2 test, and Wilcoxon signed rank sum test between cases and controls. To compare cases and controls with respect to pesticide levels, we imputed a value equal to half the limit of detection for the situation when the actual levels were found to be below the detection limit. Using these data, we performed exact Wilcoxon rank sum tests to test for differences between the distributions of pesticide levels between cases and controls. To evaluate the associations between questionnaire data and biomarkers of pesticide exposures for the risk of childhood ALL, we conducted a logistic regression analysis adjusted for other exposures such as smoking, alcohol consumption, chemicals, or medications.

Results

Forty-one of the 44 mothers (93%) of children with ALL cases, who were eligible to participate in the study approached by trained clinical research assistants, agreed to participate and fully completed the study. Specimens were collected from all the participating case pairs (mothers and their children). During the same recruitment period, we enrolled 77 mothers of children who served as noncancer controls (87% of those who were approached). All the individuals participating completed the study questionnaire and biospecimen collection.

Fifty-six percent of ALL cases were males, and the median age of the cases was 3.2 years (range 1 month to 8 years). Fifty-nine percent of the cases and 67% of the controls were white, 13% of the cases and 13% of the controls were African Americans, and 28% of the cases and 19% of the controls comprised other ethnicities (Table 1). There were no statistically significant differences between cases and control subjects in age or race and maternal or paternal smoking. Differences in household income before birth and maternal age before pregnancy varied among cases and controls.

Environmental Exposures

Environmental exposures reported by the mother are listed in Table 2. More case mothers (33%) than controls (14%) reported using insecticides in the home during the prenatal period ($P < 0.02$). Parental smoking and alcohol consumption prenatally were not significantly associated with the risk of ALL. Other environmental exposures to toxic substances such as chemicals and dyes, solvents, or medications during pregnancy did not show any significant differences between the cases and controls.

Pesticide residues were detected in 99% of urine samples obtained from mothers and from children, both from cases and from controls. In our analysis, we focused on 6 dialkyl phosphate metabolites of multiple OPs commonly found in household and garden insecticide products, including 3 dimethyl phosphates: dimethylphosphate (DMP), dimethyldi-

thiophosphate (DMDTP), and dimethylthiophosphate (DMTP) and 3 diethylphosphates: diethylphosphate (DEP), diethyldithiophosphate (DEDTP), and diethylthiophosphate (DETP). These were considered in further detail because they were detectable in most samples. Urine concentrations of the analyzed pesticide metabolites varied within the control group and within the cases. In some cases, same metabolites were found in the mother–child pairs, whereas for other families, there was no correspondence between analyte levels detected in maternal urine and its presence in the child corresponding child's urine.

The levels of DEDTP and DETP in case children were elevated compared with controls. Median DEDTP levels in children with ALL, normalized for creatinine (Cr), were 0.16 μg/gCr in comparison with 0.04 μg/gCr in controls. The levels of DEP in mothers of cases were elevated compared with controls. Median DEP levels in mothers of ALL cases were 2.51 μg/gCr compared with 1.13 μg/gCr in mothers of control subjects. Statistically significant differences were found between children with ALL and controls for DEDTP ($P < 0.05$) and DETP ($P < 0.03$). The dialkyl phosphate metabolite DMTP was detectable in most samples and was similar in cases and in controls. DMP was found in about 80% of the samples and DMDTP in about 50% of the samples and were similar in the cases and in the controls. Reported use of pesticides using the questionnaire did not correlate with the pesticide concentrations that were measured in the urine of either the mothers or the children (Table 3). A higher percentage of mothers of cases reported the use of insecticides as pest control in pets compared with mothers of controls (Table 2).

Discussion

Leukemia is the most common childhood cancer. With the exception of Down syndrome, prenatal radiation exposure, and higher birth weight, particularly for ALL, few risk factors have been firmly established. The peak of diagnosis at a young age and the presence of several translocations in neonates are suggestive of early life factor involvement in the etiology of childhood leukemia.[3–10] It has been suggested that a potential explanation for the increasing incidence rate of ALL in developed countries is pesticide exposure.[32–34]

Pesticides are ubiquitous in the environment, and 85% of US households store at least 1 pesticide for home use. Pesticides, such as OPs, are highly active biologically. Although there is growing evidence in support of an association between pesticide exposure and childhood leukemia, they are limited by ecological study designs (where exposures are inferred from data on area-wide exposures rather than information on personal-level exposures), reliance on self-reported exposures from parents, and lack of biological measurements.[35] Elevated risk has been consistently associated with no-pest strips and home use of pesticides, but associations with garden pesticide use have been mixed. Although several large studies in California found little evidence of an association between agricultural pesticide use and childhood leukemia,[34,36] these results are in contrast with the associations observed with household exposures to pesticides. The association may depend on timing of exposure, type of agent, dose, chronicity, and pathway of exposure.[37] Furthermore, some persons may be more susceptible to the effects of specific pesticides due to inherited mutations in their detoxification pathways, which may result in adverse outcomes.

In our study, reported use of pesticides using the questionnaire did not correlate with the pesticide concentrations that were measured in the urine of either the mothers or the children. The implications of these findings are that exposures to pesticides are not limited to the home and are dependent on dietary habits, exposure at day care, and metabolism. Parental exposures may depend on occupation and duration of time spent at work.

Widespread exposure to OP pesticides, the most common class of insecticides used in homes and gardens, has been documented in adults, children, and fetuses. Chronic residential use and the heavy agricultural use of these chemicals on crops, fruits, and vegetables continually expose humans to pesticides via the food chain, air, and water supply despite their short half-lives. Common pesticide exposure sources for children include dietary, dermal, and inhalational sources from foods and pesticide-treated pets and from areas in the home and yard. The exposure of children to pesticides may be greater than adults' exposure under similar circumstances due to physiological and behavioral causes. Children's skin is more permeable, their dermal contact is increased because of a proportionally larger skin surface to mass ratio, their livers have lower levels of the OP detoxification enzyme PON1,[38–40] and their hand-to-mouth behavior can increase their inadvertent chance of ingestion of pesticides.[41]

In vitro studies have shown OPs to inhibit astroglial cell proliferation and to cause neuronal apoptotic death.[42–45] These findings, and pesticide biomonitoring in inner cities and farming communities,[46,47] have led to regulatory restrictions on the use of certain OPs and have heightened concerns for their potential neurotoxic and secondary harmful effects on children.[48–51]

Our study population included males and females, females at a slightly higher ratio, and cases were matched to controls by sex and age. The known risk factors for ALL are male sex, high birth weight, and white race. The cases in our study had a higher mean birth weight of 3734.3 g compared with controls of 3399.9 g, but these differences were not statistically significant. All other parameters were similar between cases and controls besides household income, which was higher in controls than in cases. However, other indicators in our study suggest that cases with ALL came from a background where maternal education was high, most parents did not smoke, maternal body mass index was <25, and cases had no family history of cancer. In developed countries, preschool ALL (ages 1–4 years) is reported to correlate with socioeconomic status. It has been suggested that children living in areas with lowest socioeconomic status presented a significant lower risk of ALL compared with those living in the wealthiest districts, perhaps indicating that early exposure to childhood infections may decrease the risk of ALL.

Xenobiotic residues and their metabolites detected in biological fluids are an important indicator of exposure to toxic substances dispersed in the environment. Urine samples from the mother and from the children were analyzed for alkylphosphates (DMP, DMTP, DMDTP, DEP, DETP, and DEDTP), specific metabolites of OP insecticides. The compound most frequently found was DMTP, which was detectable in 99% of the subjects analyzed. The other substances were also found in both cases and controls. The source of the pesticides could be fruits, meat, and vegetables. The other variables considered (alcohol, smoking, and sampling period) seem to affect the percentages of positive values of the various substances but to different degrees.

Statistically significant differences in pesticide levels were detected between cases of ALL and controls for 2 metabolites: DETP ($P < 0.03$) and DEDTP ($P < 0.05$). DETP and DEDTP levels were higher in case children. In addition, DEP levels in mothers of cases were elevated compared with controls. Median DEDTP levels in children with ALL, normalized for creatinine (Cr), were 0.16 μg/gCr in comparison with 0.04 μg/gCr in controls. These concentrations are higher than those found in a reference sample of children of similar age in the US population (0.07 μg/gCr) in the National Health and Nutrition Examination Survey III.[52] Median DEP levels in mothers of ALL cases were 2.51 μg/gCr compared with 1.13 μg/gCr in mothers of control subjects and higher in the mothers than in a sample of women of childbearing age in the general US population (median 0.96 μg/gCr).[52]

The mechanism of acute toxicity is known for many pesticides. There are some studies of the health effects of chronic occupational exposure to some pesticides, but little is known about the long-term effects of chronic low-dose exposure, particularly for children and women during early gestation. Specifically, the role of pesticides in ALL and other cancers is not well understood at present.[53,54]

Although there is growing evidence in support of the association between pesticide exposure and childhood leukemia, most of the studies are limited by their ecological study designs, a reliance on self-reported exposures, and/or a lack of biological measurements.[21–23,55–57] The associations with garden pesticide use have been mixed.[21–23,25,58] Ma et al[58] examined the relationship between household exposures and the risk of childhood ALL and found that household pesticide use, specifically professional pest services, insecticides, and indoor pesticide, was associated with an increased risk of childhood ALL. In that study, however, exposure was based on questionnaire data alone. Although other studies found little evidence of an association between agricultural pesticide use and childhood leukemia, these results are in contrast with the associations observed with household exposures to pesticides.[21–23,25,58–60]

Variations in the associations reported in the above studies may reflect variability in issues such as timing of exposure, type of agent, dose, chronicity, and pathway of exposure. Furthermore, some persons may be more susceptible to the effects of specific pesticides due to inherited genetic mutations of enzymes in the detoxification pathways.

Case–control studies have limitations inherent to the study design. Case–control studies will not detect rare events and do not directly measure risk, the sample size is not large, and they are prone to recall bias. The case–control study has been shown to be useful for the investigation of factors to which exposure is widespread (eg, common foods or beverages), but it is of limited use for the study of uncommon types of exposure such as those associated with occupation. The case–control study is unable to detect very small relative risks (<1.5) even where exposure is widespread, and large numbers of cases of cancer are occurring in the population.

Conclusions

This study found differences in urine OP levels in children with ALL than in controls for the OP metabolites DETP ($P < 0.03$) and DEDTP ($P < 0.05$). This association of ALL risk with pesticide exposure merits further studies to confirm the association. New studies with a larger sample size are warranted to confirm our findings. The risk of ALL from gene–environment interactions remains an important issue for future research. The relationship between child health and environmental exposure to OPs is limited and has not been shown to be a causal relationship. There is therefore a need for more research, especially research based on biomarkers, of a larger sample size that includes exposures during specific time windows, exposure intensity, exposure–exposure or exposure–gene interactions, and relatively rare health outcomes such as childhood cancer.

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Table 1

Baseline Characteristics by Case–Control Status

Analysis Variable	Cases (n = 41)	Controls (n = 41)	*P*
Maternal education (%) *			0.13
≤12th grade	10 (26)	5 (13)	
Some college or technical school	7 (18)	3 (8)	
College or professional school	22 (56)	31 (79)	
Sex (%) †			
Female	23 (56)	23 (56)	—
Male	18 (44)	18 (44)	
Child's race/ethnicity (%) *			
White	22 (59)	25 (67)	0.50
Black	5 (13)	5 (13)	
Hispanic	8 (23)	7 (19)	
Other	2 (5)	0 (0)	
Maternal alcohol consumption (%) *			
Yes	20 (51)	23 (61)	0.32
No	19 (49)	15 (39)	
Paternal alcohol consumption (%) *			
Yes	24 (65)	27 (71)	0.44
No	13 (35)	11 (29)	
Maternal passive smoking (%) *			
Yes	9 (24)	6 (16)	0.32
No	29 (76)	31 (84)	
Maternal active smoking (%) *			
Yes	5 (13)	6 (16)	0.74
No	33 (87)	32 (84)	
Paternal active smoking (%) *			
Yes	12 (32)	8 (21)	0.25
No	26 (68)	30 (79)	
Maternal BMI (%) *			
<25	30 (83)	7 (17)	0.79
25–30	4 (11)	32 (80)	
>30	2 (6)	1 (13)	
Household income before birth (%) *			
≤49.99K	17 (47)	7 (18)	**0.01**
50K+	19 (53)	32 (82)	
Maternal cancer history (%) *			
Yes	6 (15)	3 (7)	0.26
No	34 (85)	37 (93)	

Analysis Variable	Cases (n = 41)	Controls (n = 41)	*P*
Paternal cancer history (%) *			
Yes	5 (12)	8 (20)	0.37
No	35 (88)	32 (80)	
Child's birth weight (g)‡	3734.3 ± 667.0	3399.9 ± 646.2	0.11
Maternal age at index pregnancy§	29.3 ± 6.3	32.0 ± 4.6	0.06
Number of child's siblings‡	1.16 ± 1.0	1.158 ± 0.9	0.90

BMI, body mass index.

*Cochran–Mantel–Haenszel test of marginal homogeneity.

†Matching factor.

‡Wilcoxon signed rank sum test.

§Paired *t* test.

Table 2

Questionnaire-Reported Parental Environmental Exposures

Characteristic	Cases, n (%)	Controls, n (%)	*P*
Maternal exposure to chemicals*	5 (12)	7 (9)	0.71
Use of insecticides as pest control in pets			
Mother	12 (33)	10 (14)	**0.02**
Father	6 (33)	9 (35)	0.99
Alcohol			
Mother	12 (47)	28 (53)	0.58
Father	17 (66)	36 (68)	0.82
Smoker			
Mother	5 (12)	11 (14)	0.88
Father	13 (30)	16 (21)	0.33

*Including dyes, solvents, adhesives, and machine oils.

Table 3

Comparison of Maternal Questionnaire Data to Urine Levels

Analysis Variable*	High Exposure, n (%)	Low Exposure, n (%)	*P*
Insect pesticide			0.34
Yes	11 (13)	6 (7)	
No	46 (56)	12 (15)	
Unknown	3 (4)	2 (5)	
Rodent pesticide			
Yes	2 (2)	2 (2)	0.54
No	51 (63)	17 (21)	
Unknown	3 (4)	1 (8)	
Weed pesticide			
Yes	0 (0)	2 (2)	**0.04**
No	55 (67)	17 (21)	
Unknown	5 (7)	1 (4)	
Fungal pesticide			
Yes	1 (1)	0 (0)	0.82
No	54 (66)	18 (22)	
Unknown	4 (5)	4 (5)	
Pet pesticide			
Yes	6 (17)	5 (14)	0.38
No	18 (50)	6 (17)	
Unknown	1 (3)	0 (0)	

*Pearson χ^2 test.