Risk Factors for Childhood Acute Non-Lymphocytic Leukemia: An Association with Maternal Alcohol Consumption during Pregnancy?[1]

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Abstract

A population-based case-control study of acute non-lymphocytic leukemia (ANLL) was performed with 80 ANLL cases diagnosed between 1973 and 1979, who were derived from the nationwide register of the Dutch Childhood Leukemia Study Group. Cases were compared to three age- and sex-matched population controls and, in order to control for recall bias, to 517 cases with acute lymphocytic leukemia from the same study base. Information on a large number of exposures to putative risk factors was collected by a self-administered questionnaire mailed to the parents. No significant association of ANLL was observed with smoking habits of the mother during pregnancy, ultrasound examinations, prenatal exposure to x-rays, viral infections, or hydrocarbon exposure. When comparing ANLL cases to population controls, maternal use of alcohol during pregnancy was associated with a more than two-fold increased risk of ANLL (odds ratio = 2.6; 95% confidence interval = 1.4–4.6). A similar increase in risk was found when comparing ANLL cases to acute lymphocytic leukemia cases. There was no significant elevation in risk for ANLL found for parental use of alcohol 1 year before pregnancy. This study suggests that intrauterine exposure to alcohol may increase the risk for childhood ANLL.

Introduction

Little is known of risk factors for childhood ANLL.[2] The incidence is low and very similar across industrialized countries. The small peak in incidence of ANLL among infants (1, 2) suggests that genetic or prenatal environmental factors including exposure to teratogens may be implicated in ANLL. Childhood ANLL has been associated with ma-

[2] The abbreviations used are: ANLL, acute non-lymphocytic leukemia; ALL, acute lymphocytic leukemia; CI, 95% confidence interval; OR, odds ratio.

ternal drug and alcohol use, parental exposure to pesticides, and congenital conditions (3–6).

Here, we present a population-based case-control study of putative risk factors for childhood ANLL including maternal and paternal alcohol consumption and smoking habits, medical history, and chemical and drug exposure during pregnancy and the year before pregnancy. We have compared 80 ANLL cases to 240 population controls. To assess recall bias, we also used 517 patients with ALL as controls.

Materials and Methods

Patients were derived from the national morbidity registration of the Dutch Childhood Leukemia Study Group. All diagnoses were made between January 1, 1973, and January 1, 1980, and were confirmed by cytomorphological examination of blood and bone marrow slides by two independent experts of the Study Group (7). For this case-control study, 713 Dutch caucasian children with leukemia (diagnosis at or before 14 years) were eligible, comprising 599 (84%) patients diagnosed with ALL, 93 patients (13%) diagnosed with ANLL, 16 (2%) patients diagnosed with chronic myeloid leukemia and 5 (1%) patients with acute unclassifiable leukemia. The response rate for ALL and ANLL patients was both 86%. The nonresponse was not associated to age, sex, or type of leukemia. Most parents indicated emotional reasons related to the loss of the child as the motivation for nonparticipation.

In the original study, for each patient one control subject was drawn from the municipal registration of the matched case (8–10). A replacement control was drawn simultaneously, who was included in the study only in case of nonresponse of the first control. The response rates for first and replacement controls were 66 and 67%, respectively. For the present case-control study on ANLL, each ANLL case was matched to two additional controls that had been matched to an ALL or CML case in the original study (8–10). Thus each ANLL case was matched to three controls according to sex and age (within 3 months).

An extensive description of the design of the study, response rates, questionnaire, and coding is given in former publications (8–10). The data were collected between October 1, 1981, and December 1, 1982, by questionnaires mailed to the children's parents. An introductory letter and three standard questionnaires with predominantly closed-ended questions (*i.e.*, requiring yes or no answers) concerning the relevant child, the natural father, and the natural mother were sent. The questionnaire concerning the child addressed the disease history of the child and siblings and the place of residence before and at the diagnosis of disease. Questions to the parents addressed alcohol consump-

tion, smoking habits, occupational history, medical history, and chemical and drug exposure during pregnancy and the year before pregnancy.

The frequency of alcohol consumption of parents during pregnancy was evaluated in closed-ended questions describing three categories: abstainers; occasional drinkers (alcohol consumption once a week); and frequent drinkers (consumption of alcohol more than once a week). Hydrocarbon exposure was assessed by job classification and by closed-ended questions in which substances were listed and parents were asked whether they had been exposed to these occupationally. Hydrocarbon-related occupations include machinist, automobile mechanic, painter, gas station attendant, laundry operator, printer, pharmacist, chemical analyst, chemical and petroleum industry worker, cleaner, and dyer. Substances containing hydrocarbons that were evaluated in closed-ended questions included dyes, paint, petroleum products, cleaning products, pesticides, herbicides, and insecticides. Paternal occupation was used as an indicator for social class. To assess medication, we asked parents whether they had used antibiotics, drugs to maintain pregnancy (mothers only), or any other drug (prescribed or nonprescribed) during or the year before the pregnancy.

In the present study, we used the OR with 95% CI to measure the strength of association. Adjusted odds ratios were calculated by conditional multiple logistic regression analysis including social class and all putative risk factors listed in Table 2 in the regression model. The effects of age and sex were controlled for by the matched design and the subsequent conditional logistic regression analysis. In the analysis comparing ALL and ANLL cases, ORs were computed in three age strata, adjusting for sex, year of birth, social class, and the putative risk factors listed in Table 2 by unconditional logistic multiple regression analysis (11).

Results from the original case-control study were only reported for ALL (8–10). After adjustment for age and sex, significantly higher odds ratios were found for the following exposures in utero: hydrocarbon exposure (OR, 2.4; CI, 2.1–4.6), x-rays (OR, 2.2; CI, 1.2–3.8), drugs to maintain pregnancy (OR, 1.6, CI, 1.0–3.5), and sedatives (OR, 2.9; CI, 1.2–7.2). With respect to medical history of the child, infectious diseases leading to hospitalization in the first year of life appeared to be inversely related to the risk of ALL (OR, 0.6; CI, 0.4–1.0). First birth conferred an increased relative risk (OR, 1.8; CI, 1.1–2.7).

Results

General characteristics of ANLL cases, ALL cases and controls are given in Table 1. ALL cases were not matched to the controls. Compared to the control children, ALL cases were slightly younger at the time of interview and more often from the medium category of social class. There was no association between social class and ANLL when comparing ANLL children and controls. Further, there were no significant differences between ANLL cases and controls with regard to first birth order (adjusted OR = 1.0; CI = 0.6–1.6), maternal age at birth at 35 years or over (adjusted OR = 1.0; CI = 0.4–2.2), and previous miscarriages (adjusted OR = 0.8; CI = 0.4–1.5) (results not shown).

In Table 2 intra-uterine exposure of ANLL cases and controls to potential teratogens are presented. The overall adjusted odds ratio of ANLL for children prenatally exposed to alcohol was 2.6 (CI = 1.4–4.6). Fewer mothers of ANLL

Table 1   General characteristic of ANLL and ALL cases and population controls

Characteristic	ANLL N = 80	ALL N = 517	Controls N = 240
Male[a]	47 (59%)	288 (56%)	141 (59%)
Age at diagnosis			
0–4 (yr)	34 (42%)	287 (56%)	
5–9	23 (29%)	149 (29%)	
10–14	23 (29%)	81 (15%)	
Mean age at interview[a]	12.6 (4.8)[b]	11.5 (4.0)	12.8 (4.9)
Social class			
Low	40 (50%)	247 (48%)	124 (52%)
Medium	12 (15%)	130 (25%)	41 (17%)
High	28 (35%)	140 (27%)	75 (31%)

[a] Matching variable for ANLL cases and controls.
[b] SD.

Table 2   Odds ratios for childhood ANLL for maternal exposure to putative teratogens during pregnancy

Risk factor	ANLL N = 80	Controls N = 240	Odds Ratio [CI]	
			Crude	Adjusted[a]
Alcohol (yes/no)	42 (53%)	83 (35%)	2.1 [1.3–3.5]	2.6 [1.4–4.6]
Occasional	32 (40%)	65 (27%)	2.0 [1.2–3.5]	2.4 [1.3–4.5]
Frequent	10 (13%)	18 (8%)	2.3 [1.0–5.4]	2.9 [1.1–7.4]
Smoking	22 (28%)	75 (31%)	0.8 [0.5–1.5]	0.6 [0.3–1.2]
Occupational exposure to hydrocarbons	3 (4%)	3 (1%)	3.1 [0.6–15.6]	3.3 [0.6–18.1]
Drug	21 (26%)	52 (22%)	1.3 [0.7–2.3]	1.2 [0.7–2.3]
To maintain pregnancy	3 (4%)	4 (2%)	2.4 [0.5–11.0]	2.5 [0.5–11.8]
Antibiotics	2 (3%)	6 (3%)	1.1 [0.2–5.4]	1.0 [0.2–5.7]
Ultrasound	3 (4%)	8 (3%)	1.1 [0.3–4.4]	1.1 [0.2–5.2]
Radiation (x-rays)	6 (8%)	8 (3%)	2.4 [0.8–7.0]	1.7 [0.6–5.3]
Viral infections	2 (3%)	4 (2%)	1.5 [0.3–8.4]	1.0 [0.2–5.7]

[a] Adjusted by conditional logistic regression analysis for effects of gender, age, social class, and all other putative risk factors for ANLL listed.

cases than control mothers reported smoking during pregnancy while more mothers of ANLL cases reported to be exposed during pregnancy to hydrocarbons occupationally, drugs to maintain pregnancy, and X-rays. None of these differences reached statistical significance.

In Table 3, alcohol use during pregnancy of mothers of ANLL cases is compared to the use of mothers of ALL cases and controls. Cases are stratified by the age at diagnosis; control children are stratified by the age at diagnosis of the matched ANLL case. A statistically significant excess risk of

Table 3 Odds ratios of childhood ANLL and ALL for use of alcohol during pregnancy, stratified by age at diagnosis

Age at diagnosis (yr)	Maternal use	ANLL, N = 80	ALL, N = 517	Controls, N = 240	Odds ratios[a] [CI]		
					ANLL vs. controls	ALL vs. controls	ANLL vs. ALL
0–4	Yes	21 (62%)[b]	115 (40%)	36 (35%)	2.8	1.1	2.1
	No	13 (38%)	172 (60%)	66 (65%)	[1.2–6.5]	[0.8–1.9]	[1.4–4.4]
	Total	34 (100%)	287 (100%)	102 (100%)			
5–9	Yes	15 (65%)	51 (33%)	26 (38%)	3.0	0.8	3.3
	No	8 (35%)	105 (67%)	43 (62%)	[1.1–8.4]	[0.5–1.5]	[1.7–9.4]
	Total	23 (100%)	156 (100%)	69 (100%)			
10–14	Yes	6 (26%)	22 (30%)	21 (30%)	0.8	1.0	0.9
	No	17 (74%)	52 (70%)	48 (70%)	[0.3–2.3]	[0.4–2.1]	[0.4–2.2]
	Total	23 (100%)	74 (100%)	69 (100%)			

[a] Adjusted by logistic regression analysis for effects of sex, age, date of birth (not in the comparison of ANLL vs. controls due to the matching), social class, and all other putative risk factors for ANLL listed in Table 2.
[b] Percentage of total in age category.

ANLL for maternal use of alcohol during pregnancy was found in the strata 0–4 years and 5–9 years, when comparing ANLL cases to controls as well as to ALL cases. No statistically significant association between ALL and maternal alcohol consumption during pregnancy was found. For none of the other putative risk factors for childhood leukemia listed in Table 2 were differences in exposure found when comparing ANLL cases to ALL cases.

No significant elevation in risk was found for parental use of alcohol 1 year before pregnancy. The odds ratios for paternal and maternal use of alcohol 1 year before pregnancy were 1.5 (CI = 0.6–3.5) and 1.2 (CI = 0.7–2.3), respectively. Neither was parental exposure in the year prior to the pregnancy to one of the other potential risk factors (listed in Table 2) associated to the risk of childhood ANLL.

Discussion

In this case-control analysis, we have investigated a great number of putative risk factors for ANLL. No significant association of ANLL was observed with smoking habits of the mother during pregnancy, ultrasound examinations, prenatal exposure to x-rays, viral infections, or hydrocarbons. However, exposure frequencies were low in the present study and more mothers of ANLL cases than control mothers reported to be exposed during pregnancy to hydrocarbons occupationally, to drugs to maintain pregnancy, and to x-rays, while fewer mothers of ANLL cases reported smoking during pregnancy. A significantly increased risk of ANLL for maternal use of alcohol during pregnancy was observed, independent of social class and other potential risk factors for childhood leukemia. No significant elevation in risk of ANLL was found for parental use of alcohol 1 year before pregnancy.

A limitation of our study is that because of the retrospective data collection, detailed information on the absolute quantity of alcoholic drinks consumed could not be assessed. Further, we do not have information on changes of alcohol consumption during pregnancy. However, frequency of alcohol use (yes/no) reported by control mothers was similar to that of previous studies (12, 13). Another methodological issue to be discussed is that in this study we relied heavily on the self-reported alcohol intake in the past. Since cases and controls were matched for age, the diffi-

culty in recalling information during pregnancy was similar for the matched pairs. Therefore this type of misclassification and the ones discussed earlier in this paragraph are expected to be random and to dilute the difference between cases and controls rather than to cause spurious associations. Associations may be introduced artificially by recall and exposure suspicion bias (14). Parents of patients may be more willing to recollect exposures than parents of controls. We could overcome this problem by comparing ANLL patients to ALL patients. Finally, selection bias seems unlikely since the present study covered over 95% of children with leukemia in The Netherlands diagnosed between 1973 and 1980, and all diagnoses of ANLL and ALL cases were confirmed by cytomorphological examination of bone marrow preparations by a central laboratory (15). As for the control children, the first control and the replacement subject were selected simultaneously and their response rates were similar.

The present study suggests that prenatal exposure to alcohol is associated with childhood ANLL. A critical concern regarding false positive associations results from multiple comparisons which were made in this study. However, our findings are supported by an earlier study which suggested an excess use of alcohol during pregnancy by mothers of cases with childhood ANLL diagnosed before the age of 2 years (6). Our data suggest an increase in risk of ANLL diagnosed up to 10 years. In the present study, alcohol was associated specifically to ANLL and not to ALL (see also previous analysis, Ref. 9). We could show no evidence for an increase in risk of ANLL for maternal alcohol consumption in the year before the pregnancy. As the increase in risk of ANLL was confined to maternal alcohol use during pregnancy, our findings are compatible with a teratogenic effect. The mechanism through which alcohol may be related to childhood ANLL is unclear. Although numerous adverse effects of maternal alcohol use during pregnancy on offspring have been reported (16–22), experimental and clinical studies have provided no direct evidence for a link to ANLL. Therefore, we cannot exclude the possibility fully that an unknown confounding variable that is associated to alcohol intake as well as to the risk of ANLL may explain the observed association.

An increased risk of childhood ANLL has been reported for prenatal exposure to pesticides and maternal

drug use (3, 4). We observed an increase in risk of ANLL, albeit nonsignificant, for maternal exposure during pregnancy to hydrocarbons occupationally, to drugs to maintain pregnancy, and to x-ray exposure (8–10). In contrast to studies of ALL, we have found no association of ANLL with high social class, first birth order, late maternal age, and habitual abortion (23–27).

In conclusion, our study supports an earlier finding of an association of maternal use of alcohol during pregnancy with childhood ANLL. The findings of the present study are compatible with a teratogenic effect of alcohol, as no association was found to alcohol use in the year before pregnancy. Finally, our study suggests that alcohol may specifically increase the risk for childhood ANLL and not for ALL.

Acknowledgments

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