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ORIGINAL PAPER

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Parental Occupational Exposures and Risk of Childhood Acute Leukemia

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ABSTRACT

Introduction: Acute leukemia, accounting for 20% of all cancers diagnosed in individuals younger than 19 years old, is the most prevalent childhood malignancy. Among environmental risk factors, parental occupational exposures have attracted scientific interest as potential predisposing factors for childhood leukemia. The role of parental occupational exposure to social contacts, harmful chemicals, electromagnetic fields and ionizing radiation has been investigated with conflicting and inconsistent results. **Aim:** A case-control study aiming to assess the association between parental occupational exposures to social contacts, chemicals and electromagnetic fields and the risk of offspring acute leukemia. **Material and Methods:** 108 children with acute leukemia and equal number of matched controls were included. Data on parental occupations before conception, during pregnancy, during breastfeeding and after birth, and on potential risk factors was recorded. Associations between parental exposure and risk of childhood leukemia were estimated. **Results:** Parental occupational exposure during the four periods of exposure was not associated with childhood leukemia. High birth weight and family history of cancer were associated with the development of childhood acute leukemia. A weak association of maternal medication use during pregnancy and leukemia risk emerged. **Conclusions:** Since the causative factors of childhood leukemia remain unknown, further investigation is mandatory for the reduction of disease burden.

Keywords: Childhood acute leukemia, electromagnetic fields, harmful chemicals, occupational exposures, risk factors, social contacts.

19 years old, is the most prevalent childhood malignancy (1). Several epidemiologic studies have investigated potential risk factors for acute leukemia in children including genetic, infectious, and environmental. Ionizing radiation and certain genetic characteristics are the only established risk factors for childhood leukemia, whereas other lifestyle or environmental parameters have been suggested as causal agents with compelling evidence (2).

Among environmental risk factors, parental occupational exposures have attracted scientific interest as potential predisposing factors for childhood leukemia. The biological mechanisms linking occupational exposure with the risk of leukemia in the offspring remain largely unclear. Similarly, there is lack of understanding regarding the effect of the time frame of exposure. It has been proposed that chemicals may increase the risk of childhood leukemia prior to conception by damaging parental germ cells, during pregnancy through transplacental transfer from the parents to the index child, or postnatal through breastfeeding, through the inhalation of solvents from parents' skin and clothing and through the exhaled air (3, 4).

A number of studies have explored the association between different occupational exposures of either parent and the risk of leukemia in their offspring. The role of parental occupational exposure to social contacts, harmful chemicals, electromagnetic fields and ionizing radiation has been investigated with conflicting and inconsistent results, as subsequently discussed. Except for the relatively strong evidence for parental exposure to pesticides and to infections, no other environmental factors have been established as major contributors of childhood leukemia burden worldwide (5).

Given the inconsistency between previous findings and the increased incidence rate of

1. INTRODUCTION

Acute leukemia, accounting for 20% of all cancers diagnosed in individuals younger than

childhood acute leukemia in Greece, we conducted a study in a major pediatric Greek hospital aiming to investigate the potential association between parental occupational exposures and the development of acute leukemia in the offspring. As a secondary objective of our study, the contribution of other potential risk factors to leukemia risk was analyzed.

2. AIM

A case-control study aiming to assess the association between parental occupational exposures to social contacts, chemicals and electromagnetic fields and the risk of offspring acute leukemia.

3. MATERIAL AND METHODS

This is a case-control study conducted at the General Children's Hospital "P. & A. Kyriakou", a major pediatric hospital of Athens, Greece. Cases were 108 children under the age of 15, who visited or were hospitalized at the Oncology Department and were diagnosed with acute lymphoblastic or acute myeloid leukemia. The control group consisted of an equal number of children who were admitted to the Second Pediatric Department for acute conditions during the same period of time and were not diagnosed with leukemia or other malignancies. Cases and controls were matched for age, gender and ethnicity.

Data collection

A written questionnaire was developed to obtain information on parental occupation during four specific periods of time, namely 1 year before conception, during pregnancy, during breastfeeding and from the end of breastfeeding until diagnosis. The time periods were selected with the aim to reveal the potential biological mechanisms through which parental occupational exposure may provoke the development of acute leukemia in the offspring. Both parents recorded all full or part-time jobs that lasted over 6 months as well as any agricultural activities carried out on a part-time basis. The questionnaire also contained information on demographic characteristics (age at diagnosis, gender and ethnicity of the child) and on other factors potentially associated with childhood acute leukemia. The parameters investigated included family history of cancer, birth weight, residence in an urban or a rural area, daycare attendance, parental age at birth, parental educational level, maternal medication use during pregnancy, parental alcohol consumption 1 year before conception and during pregnancy, parental smoking 1 year before conception, during pregnancy and after pregnancy, birth order and duration of maternal occupation at pregnancy. The cutoffs for birth weight and parental age were determined as in previous studies (6-8). Family history of cancer refers to the diagnosis of malignancies at children's first and second degree relatives. Potential associations between parental smoking and alcohol consumption and leukemia risk were evaluated based on the time windows applied by Perez-Saldivar (6), with the addition of the time period "during pregnancy".

Questionnaires were identical for case and control parents, and all interviews were carried out by a single trained interviewer. The protocol of the study was approved by the Scientific Council of "P. & A. Kyriakou" hospital and the

content of the questionnaire was approved by the clinical psychologist of the Oncology Department. All parents provided written or verbal permission for the interview, with the exception of two parents of cases and four control parents who were unwilling to participate.

Occupational coding and grouping

The job titles obtained during the interviews were coded according to the International Classification of Occupations (ISCO-08) of the International Labor Organization (ILO) (9), so that findings would be comparable to those from other European studies. The four-digit codes corresponding to the reported occupations were subsequently grouped into four occupational exposure groups, specifically high contact level, chemicals, electromagnetic fields and ionizing radiation. This classification is based on data from the literature and was appropriately adjusted according to the knowledge and experience of the Occupational and Industrial Hygiene Department of the National School of Public Health of Greece. The occupational exposure group of social contacts is based on the classification applied by Kinlen and Bramald (10), but the categories high and very high contact level were incorporated in one group indicated as "high contact level". The occupational exposure group of chemicals is associated with specific potentially harmful chemicals as listed in the study of Fear et al (11). Exposure variables were created separately for paternal and maternal exposure and for each time period examined.

Statistical Analyses

Statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS). Conditional regression analysis was performed for each occupational exposure group and each period of exposure, separately for fathers and mothers. Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated as presented. In addition to the matching variables (age of the child at diagnosis, gender and ethnicity), other potential confounding factors previously reported by Perez-Saldivar et al (6) were included in the applied model. These are family history of cancer, paternal and maternal age at child's birth, paternal and maternal alcohol consumption and smoking, and child's birth weight. χ^2 -test, t-test and Mann-Whitney-test were used as appropriate to investigate associations between potential risk factors and childhood acute leukemia.

4. RESULTS

The results of our study are presented in Tables 1 and 2. Table 1 displays the frequency distributions of the demographic characteristics of the cases, and the odds ratios and 95% confidence intervals for the risk of childhood acute leukemia in relation to specific potential predisposing factors. The vast majority of cases (86.1%) were diagnosed with acute lymphoblastic leukemia, as expected. Among potential risk factors, birth weight of 3500g or more and positive family history of cancer were associated with the development of acute leukemia (OR: 2.27 and 1.85, respectively). A weak negative association was observed between maternal medication use and smoking during pregnancy and childhood leukemia risk (OR: 0.46 and 0.58, respectively). There was some weak evidence that the risk of the disease increases with paternal smoking and alcohol consumption

| Variables | Cases (N=108) | | Controls (N=108) | | Crude OR ^a [95% CI ^b] |
|--------------------------------------------------------------------|------------------|------|---------------------|------|-------------------------------------------------|
| | N | % | N | % | |
| Type of leukemia | | | | | |
| ALL ^c | 93 | 86.1 | | | |
| AML ^d | 9 | 8.3 | | | |
| Gender: Male | 63 | 58.3 | | | |
| Ethnicity: Greek | 94 | 87.0 | | | |
| Age at diagnosis: 2-6 years old | 64 | 59.3 | | | |
| Family history of cancer | 52 | 48.1 | 37 | 34.3 | 1.85 [1.07-3.20] |
| Birth weight: ≥ 3500g | 47 | 43.5 | 29 | 26.9 | 2.27 [1.27-4.04] |
| Residence in an urban area (≥2.000 residents) | 79 | 73.1 | 82 | 75.9 | 0.86 [0.47-1.59] |
| Ever-attendance of day care | 48 | 44.4 | 52 | 48.1 | 0.86 [0.50-1.47] |
| Paternal age at birth: >35 years | 37 | 34.3 | 41 | 38.0 | 0.85 [0.49-1.49] |
| Maternal age at birth: >35 years | 19 | 17.6 | 24 | 22.2 | 0.75 [0.38-1.46] |
| Paternal educational level: >9 years | 67 | 62.0 | 66 | 61.1 | 1.04 [0.60-1.80] |
| Maternal educational level: >9 years | 78 | 72.2 | 74 | 68.5 | 1.20 [0.67-2.14] |
| Maternal medication use during pregnancy | 21 | 19.4 | 37 | 34.3 | 0.46 [0.25-0.86] |
| Paternal alcohol consumption ^e 1 year before conception | 64 | 59.3 | 51 | 47.2 | 1.63 [0.95-2.79] |
| Paternal alcohol consumption ^e during pregnancy | 64 | 59.3 | 50 | 46.3 | 1.69 [0.98-2.89] |
| Maternal alcohol consumption ^e 1 year before conception | 19 | 17.6 | 19 | 17.6 | 1.00 [0.50-2.02] |
| Maternal alcohol consumption ^e during pregnancy | 2 | 1.9 | 4 | 3.7 | — ^f |
| Paternal smoking ^g 1 year before conception | 63 | 58.3 | 60 | 55.6 | 1.12 [0.65-1.92] |
| Paternal smoking ^g during pregnancy | 59 | 54.6 | 57 | 52.8 | 1.08 [0.63-1.84] |
| Paternal smoking ^g after pregnancy | 57 | 52.8 | 52 | 48.1 | 1.20 [0.71-2.05] |
| Maternal smoking ^g 1 year before conception | 43 | 39.8 | 43 | 39.8 | 1.00 [0.58-1.72] |
| Maternal smoking ^g during pregnancy | 14 | 13.0 | 22 | 20.4 | 0.58 [0.28-1.21] |
| Maternal smoking ^g after pregnancy | 9 | 8.3 | 7 | 6.5 | 1.31 [0.47-3.66] |
| Paternal agricultural activities | 25 | 23.1 | 26 | 24.1 | 0.95 [0.51-1.78] |
| Maternal agricultural activities | 9 | 8.3 | 11 | 10.2 | 0.80 [0.32-2.02] |

Table 1. Demographic characteristics of patients and association between potential risk factors and childhood acute leukemia. a: odds ratio, b: confidence interval, c: acute lymphoblastic leukemia, d: acute myeloid leukemia, e: ≥2 drinks per week, f: Chi-square test was not applicable due to the small number of mothers who consumed alcohol during pregnancy, g: ≥1 cigarette per week for ≥6 month

during most of the exposure time periods, even though not significant. Since a very limited number of women (4 mothers of cases and 2 mothers of controls) consumed 2 or more drinks per week during pregnancy, statistical analysis of this variable was unattainable. The remaining risk factors examined showed no association with the development of acute leukemia in children, including urban or rural residence, birth order, daycare attendance, parental age and educational level or agricultural activities.

Table 2 presents conditional logistic regression-derived odds ratios and 95% confidence intervals for the risk of childhood acute leukemia in relation to occupational exposure groups. Data were separately analyzed for paternal and maternal exposure as well as by time period of exposure. High levels of paternal social contacts at work were not as-

sociated with an elevated risk of childhood acute leukemia during any of the four exposure time periods. High levels of maternal social contacts, only after birth and mainly during breastfeeding, were weakly and not significantly associated with an increased risk of leukemia in the offspring. As for occupational exposure to chemicals either paternal or maternal, no associations emerged regardless of the time period of exposure. Paternal exposure to electromagnetic fields at all time periods did not appear to contribute to the development of childhood acute leukemia. Regression analysis was not applicable for the investigation of the potential associations between parental exposure to ionizing radiation and maternal exposure to electromagnetic fields and the risk of childhood leukemia because of the small number of exposed parents.

| Occupational exposure groups | Cases (N=108) | | Controls (N=108) | | Crude OR ^a [95% CI ^b] |
|------------------------------------|------------------|------|---------------------|------|-------------------------------------------------|
| | N | % | N | % | |
| High contact level | | | | | |
| Maternal exposure | | | | | |
| 1 year before conception | 53 | 49.1 | 53 | 49.1 | 0.95 [0.53-1.71] |
| During pregnancy | 37 | 34.3 | 34 | 31.5 | 1.00 [0.53-1.90] |
| During breastfeeding | 12 | 11.1 | 5 | 4.6 | 2.04 [0.61-6.79] |
| From child's birth until diagnosis | 53 | 49.1 | 44 | 40.7 | 1.46 [0.80-2.65] |
| Paternal exposure | | | | | |
| 1 year before conception | 33 | 30.6 | 33 | 30.6 | 1.00 [0.53-1.88] |
| During pregnancy | 32 | 29.6 | 34 | 31.5 | 0.93 [0.50-1.75] |
| During breastfeeding | 32 | 29.6 | 33 | 30.6 | 0.97 [0.51-1.81] |
| From child's birth until diagnosis | 37 | 34.3 | 38 | 35.2 | 0.93 [0.50-1.72] |
| Chemicals | | | | | |
| Maternal exposure | | | | | |
| 1 year before conception | 21 | 19.4 | 24 | 22.2 | 0.73 [0.36-1.52] |
| During pregnancy | 14 | 13.0 | 12 | 11.1 | 1.14 [0.47-2.78] |
| During breastfeeding | 3 | 2.8 | 5 | 4.6 | 0.36 [0.07-2.04] |
| From child's birth until diagnosis | 22 | 20.4 | 20 | 18.5 | 1.02 [0.47-2.21] |
| Paternal exposure | | | | | |
| 1 year before conception | 66 | 61.1 | 66 | 61.1 | 0.88 [0.48-1.60] |
| During pregnancy | 67 | 62.0 | 67 | 62.0 | 0.88 [0.48-1.60] |
| During breastfeeding | 67 | 62.0 | 65 | 60.2 | 0.94 [0.52-1.71] |
| From child's birth until diagnosis | 65 | 60.2 | 69 | 63.9 | 0.78 [0.43-1.44] |
| Electromagnetic fields | | | | | |
| Paternal exposure | | | | | |
| 1 year before conception | 6 | 5.6 | 6 | 5.6 | 1.49 [0.42-5.35] |
| During pregnancy | 6 | 5.6 | 6 | 5.6 | 1.49 [0.42-5.35] |
| During breastfeeding | 6 | 5.6 | 6 | 5.6 | 1.49 [0.42-5.35] |
| From child's birth until diagnosis | 6 | 5.6 | 6 | 5.6 | 1.58 [0.45-5.46] |

Table 2. Association between parental occupational exposures and childhood acute leukemia during four periods of exposure. a: odds ratio, b: confidence interval

5. DISCUSSION

The aim of our study was to investigate the potential association between parental occupational exposures and the risk of acute leukemia in the offspring in the Greek population. We specifically assessed paternal exposure to social contacts, chemicals and electromagnetic fields, and maternal exposure to social contacts and chemicals. Our assessment was extended to four time periods of exposure, namely preconceptionally, during pregnancy, during breastfeeding, and after birth until diagnosis. Our findings provide no evidence of an association between paternal occupational exposure to social contacts, chemicals or electromagnetic fields and the risk of acute childhood leukemia either prior to conception, during pregnancy or after birth. We present some evidence of an association between maternal exposure to social contacts during breastfeeding and leukemia risk. Additionally, our findings support the potential role of high birth weight and family history of cancer as predisposing factors for the development of acute leukemia. We also report a potential protective effect of maternal medication consumption during pregnancy against disease development.

Fairly limited data are currently available regarding the effect of parental occupational social contacts to offspring leukemia risk. Studies have assessed only paternal exposure and do not support its association with the development of the disease (11, 12), with the exception of some weak indi-

cations of a positive association specifically in rural areas (10). A number of factors may contribute to inconsistencies between study results, primarily differences in population mixing, in the classification of the degree of occupational contact and in the investigated time periods. Overall, data do not support an association between parental occupational social contacts and offspring leukemia risk, in agreement with our findings. However, we provide some evidence that high levels of maternal social contacts during breastfeeding may contribute to the development of childhood acute leukemia. Assuming that occupational social contact can be applied as a surrogate marker of infection, our observation seems reasonable and worthy of further investigation.

A major drawback in the assessment of the contribution of occupational chemical exposure to cancer risk is that chemicals cover a wide spectrum of substances with variable effects, introducing significant inconsistency between research findings. A number of studies have investigated the potential association between parental occupational exposure to chemicals and the risk of childhood leukemia, but they are characterized by marked differences in the methodological approach, the recruited populations, the time frame of exposure and the categorization of chemicals. Thus, evidence for any association falls short of certainty. The strongest evidence suggests that preconceptional, during pregnancy and prenatal parental exposure to specific chemicals and pesticides increases the risk of childhood

leukemia (6, 13). In agreement, a meta-analysis concluded that childhood leukemia was associated with prenatal parental exposure to pesticides, with the strongest evidence for maternal exposure (14). Similarly, there is some evidence that maternal exposure to paints, lacquers and hydrocarbons prior to conception and during pregnancy may be associated with cancer risk in the offspring (15). More specifically, Shu et al observed associations between paternal and maternal exposure to a variety of agents and the presence of mutations in the K-ras and N-ras genes, leading them to the hypothesis that parental exposure to specific chemicals may be associated with distinct ras mutations in children that contribute to the development of leukemia (16). Considering that our study investigated a broad category of harmful chemicals, the absence of significant associations between parental exposure and childhood leukemia risk is somewhat expected. Nevertheless, the effect of each potentially harmful chemical cannot be excluded.

Parental exposure to electromagnetic fields has been previously investigated as a risk factor for childhood leukemia with variable findings. The lack of consistency between findings can be partly attributed to the fact that studies have applied different methodologies for exposure assessment. Most studies have inferred exposure to electromagnetic fields by the job title or by relating a job title to a job exposure matrix, and are considered less accurate as they are prone to misclassification. On the contrary, the assignment of the exposure based on the tasks performed in each job by a group of experts is considered a more appropriate methodology (17). A limited number of studies, conducted by assigning exposure from the job title or relating a job title to a matrix, found a positive association between paternal exposure and offspring leukemia risk (18, 19). Contradictory data have emerged, regarding maternal exposure, an association with a moderately increased risk (20) while other no association (21). In agreement, more recent large case-control studies concluded that pre- and postconceptional paternal and maternal exposure to low-frequency magnetic fields is not linked to increased childhood leukemia risk (17, 22). Our findings on paternal exposure to electromagnetic fields also indicate no association with the development of leukemia in the offspring, in support of aforementioned studies.

As a secondary objective of our study, we investigated the effect of certain demographic and lifestyle parameters as potential risk factors of childhood acute leukemia. The strongest association emerged for the increased birth weight of >3500 g. High birth weight, 4000 g or larger, is nowadays recognized as an established risk factor for childhood leukemia, especially acute lymphoblastic leukemia (23, 24). According to the proposed hypothesis, the increased birth weight may be associated with a high rate of cell proliferation and consequently with an increase in the precursor cells at risk for malignant transformation (25). We also observed a positive association between family history of cancer and childhood acute leukemia. Other studies on family history of cancer and childhood acute lymphoblastic leukemia provide inconsistent findings. Most show no increased risk, but associations with specific cancer sites have also been reported (26, 27). It is noteworthy that all

these studies present significant methodological differences regarding design, data collection and assessment with unknown effect on the derived conclusions. It is evident that more large-scale well-controlled studies are required to provide insight into the role of family history of cancer as a potential risk factor.

Interestingly, we observed an inverse association between maternal medication use and smoking during pregnancy and childhood leukemia risk. Maternal consumption of vitamin, folate or iron supplements has been associated with a reduced risk of non-Hodgkin lymphoma and leukemia (28, 29). In our study, no specific information on medication was reported, thus no further conclusions can be deduced. Further analysis considering specific categories and types of medication are expected to further clarify their potential effect on disease development. As for smoking, our finding are in good agreement with the fairly consistent evidence that maternal cigarette smoking before and during pregnancy is not associated with childhood leukemia risk (30). Nevertheless, whether weakly or strongly associated with cancer and the overall state of health, unhealthy environmental conditions and lifestyle habits are discouraged.

The main limitation of our study is the moderate sample size, due to which the potential contribution of parental occupational exposure to ionizing radiation and of maternal exposure to electromagnetic fields could not be assessed. Despite this, our findings are in good agreement with other studies conducted on much larger populations. Limitations related to biases characterizing case-control studies and the use of hospital-based controls should not be omitted. Like other studies with similar design, this study is subject to exposure misclassification within each occupation due to inter-individual variability. A misclassification of individual exposure status is more likely for occupations with a low prevalence of exposure, introducing bias. However, the classification of occupations into exposure groups is an established methodology that unifies jobs related to similar kinds of exposure, so that conclusions concerning exposures can be extracted. In our study, occupational exposure to harmful chemicals was investigated for a group of agents and corresponding analysis for single substances was not possible. Similarly, exposure to electromagnetic fields was assigned by job title introducing bias. Nevertheless, a major strength of our study is that classification of occupational exposure relied on the knowledge and experience of an expert. While we investigated the effect of parental occupational exposure to social contacts, chemicals and electromagnetic fields individually, we cannot preclude the possibility that parental cumulative exposure may have an etiologic role in the development of acute leukemia in the offspring. The analysis of parental exposure during four distinct time periods is another advantage of our study, since typically less than three periods of exposure are applied. However, there is lack of information on duration of each occupation thus this parameter was not analyzed.

6. CONCLUSION

In conclusion, our study provides no evidence of an association between parental occupational exposure to social contacts, harmful chemicals and electromagnetic

fields with the risk of childhood acute leukemia, in agreement with previous studies. Our analysis of potential risk factors indicates that increased birth weight and positive family history of cancer may predispose to the development of the disease. We also present some evidence of a negative association with maternal medication use during pregnancy which merits further investigation. Since the causative factors of childhood leukemia remain unknown, further investigation is mandatory and a crucial step for the reduction of the burden of the disease.

- **Key points (Clinical significance):** We investigated the controversial issue of the contribution of parental occupational exposures to the development of acute leukaemia in the offspring, and potential risk factors which may lead to this malignancy. Birth weight of ≥ 3500 g and positive family history of cancer seem to increase the risk of childhood acute leukemia. Maternal medication use during pregnancy may have a protective role against disease development.
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