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The risk profile of childhood leukaemia in Greece: a nationwide case–control study

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Summary The risk profile of childhood leukaemia in Greece was studied through a case–control investigation that included all 153 incident cases of the disease, ascertained throughout the country during 1993 and 1994, and two hospital controls for every case matched for gender, age and place of residence. The data were analysed using conditional logistic regression and the associations are expressed in terms of adjusted odds ratios (OR) and their 95% confidence intervals. Cases were born to mothers of a higher standard education, the OR for an increment of four schooling years being 1.48 (1.17–1.87) and had higher birth weight, the OR for an increment of 500 g being 1.36 (1.04–1.77). Pet ownership and birth after a pregnancy with anaemia were associated with increased risk, the ORs being 2.18 (1.14–4.16) and 2.60 (1.39–4.86) respectively. From the frequency analyses, indicative inverse associations were found with birth order, household crowding and previous hospitalization with allergic diseases, whereas indicative positive associations were found with diabetes mellitus during pregnancy and with neonatal jaundice. Substantial or significant elevations were not found with respect to maternal smoking and coffee drinking during pregnancy, diagnostic radiography and ultrasonographic examinations or blood transfusions. A significant inverse association with maternal consumption of alcohol could be due to multiple comparisons, but a detrimental effect can probably be excluded. A non-significant positive association with total shots of viral vaccinations and a weak non-significant inverse association with breast feeding were also found. We interpret the findings of this study as being compatible with acute childhood leukaemia being linked with delayed development of herd immunity to fairly common infectious agents, in conjunction with accelerated perinatal and early post-natal growth.

Keywords: childhood leukaemia; birthweight; herd immunity; pet ownership

The aetiology of childhood leukaemia remains an enigma. Ionizing radiation is an established cause (US National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation, 1990), but it is unlikely to explain more than a small fraction of all cases (probably less than 20%). Epidemiological studies throughout the world have explored several groups of factors, and the collective evidence has recently been summarized (Chow et al, 1996; Linet & Cartwright, 1996). Infectious agents remain prime candidates because of the animal evidence and the role of HTLV-I in a rare form of leukaemia (Mueller, 1991), but opinions diverge as to whether a specific virus is implicated or whether common infectious agents are responsible, their effect conditioned by particular genotypes or certain patterns of herd immunity (Kinlen et al, 1990, 1995; MacMahon, 1992; Greaves and Alexander, 1993; Petridou et al, 1993; Kinlen, 1995; Greaves, 1997). Paradigms from other diseases have stimulated searches for prenatal viral (Curnen et al, 1974; Randolph and Heath, 1974; Fine et al, 1985) and chemical exposures (Cutler et al, 1986; Lowengart et al, 1987; Shu et al, 1988; Robison et al, 1989; Savitz and Chen, 1990; Zack et al, 1991), but these results have been collectively unconvincing (Chow et al, 1996). Research focusing on post-natal chemical exposures, including diet, vitamins and drugs (Shu et al, 1988; Olsen et al, 1994; Peters et al, 1994; Sarasua and Savitz, 1994) – with the possible exceptions of chemotherapy (Pui et al, 1991) and administration of growth hormone (Ritzen, 1993) – has also been inconclusive. Studies of correlates of perinatal growth, notably birth weight, have generated intriguing results, but the nature of the underlying processes and the preventive implications of these findings remain elusive (MacMahon and Newill, 1962; Daling et al, 1984; Robison et al, 1987; Zack et al, 1991). Types of radiation other than ionizing have also been investigated, including extremely low frequency electric and magnetic fields (ELF, EMF) (Oak Ridge Associated Universities, 1992; National Research Council, 1996), radiofrequency waves (Maskarinec, 1994), phototherapy (Ben-Sasson and Davis, 1992; Miller, 1992) and diagnostic ultrasounds (Shu et al, 1994), but the evidence is contradictory.

Certain correlation studies in Greece have provided evidence for an infectious aetiology of childhood leukaemia (Kinlen and Petridou, 1995; Petridou et al, 1996*a*) and an earlier case–control investigation that has no overlap with the present study also

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pointed in the same direction (Petridou et al, 1993). During 1993–94 we undertook a nationwide study to ascertain the risk factors for childhood leukaemia in this country. A study protocol similar to that used in ongoing case–control investigations in other European countries was used. Blood samples were also collected, and sera and bone marrow slides have been preserved for the evaluation of any new hypothesis that may be proposed in the near future.

SUBJECTS AND METHODS

During the 2-year period 1993–94, 153 bone marrow confirmed cases of childhood (aged 0–14 years) leukaemia were diagnosed through a nationwide network of childhood haematologists/oncologists giving an incidence of 41.8 cases per 10^{-6} person–years. This rate is similar to or slightly higher than rates observed in other developed countries. Of these cases, 136 (89%) were of the acute lymphoblastic type. Ascertainment of incident childhood leukaemia cases is thought to be virtually complete, with the exception of a few cases that were diagnosed and treated abroad (Petridou et al, 1996*a* and *b*). Nine additional children with leukaemia were not eligible for the study because they were not of Greek nationality.

For every case the first two hospital controls that met with preset matching criteria were enrolled in the study. Controls had to be hospitalized at the same time as the corresponding cases for acute conditions; be of the same gender and age (± 6 months for cases younger than 3 years and ± 12 months for older children) and, for urban areas, reside at the time of diagnosis in the same town or, for rural residents, at any village in the same geographic region.

The guardians of all cases (95% mothers) and controls (96% mothers) were informed of the study objectives and were asked to respond to an interviewer-administered questionnaire concerning sociodemographic, environmental, lifestyle and biomedical variables and to allow a blood sample to be taken from the child for serum preservation. There were no refusals from the guardians of the cases but the guardians of 14, otherwise eligible, controls (4%) were unable or unwilling to participate, and eight of them were replaced.

Measures of electric and magnetic field exposure were ascertained blindly for cases and controls through collaboration with the Public Power Corporation (PPC). Relevant results as well as those derived from serological tests will be reported separately. Frequency distributions of the different variables were examined initially and the data were then modelled using conditional logistic regression (Breslow and Day, 1980). Unconditional regression with additional terms for the matching factors generated very similar results. Given the weak overall associations, we opted against using stepwise regression because this could have left substantial residual confounding (MacMahon and Trichopolos, 1996).

RESULTS

Table 1 presents frequency distributions of cases and controls by sociodemographic, lifestyle, environmental and biomedical variables. In the same table the bivariate associations are evaluated and the respective *P*-values, derived from χ^2 with one degree of freedom, are given. A plus or minus sign indicates a positive or inverse association, respectively, considering in all instances the first of the indicated categories as unexposed or less exposed. The patterns in this table are indicative but they are not aetiologically interpretable in strict terms because of mutual confounding and the underlying matching.

Table 2 shows conditional logistic regression-derived, mutually adjusted odds ratios for childhood leukaemia in specific exposure categories or by specified increments in the study variables. There was a highly significant positive association with level of maternal education ($P = 0.001$). It appears also that the risk of childhood leukaemia increases with maternal age at birth and sibship size and decreases with increasing birth order; however, these patterns are not statistically significant. Day care attendance and household crowding, proxies for infectious agent transmission at an early age, are associated with slightly reduced risk but again neither of these associations is statistically significant. Among lifestyle variables, pet ownership at any time before diagnosis (cases) or interview (controls) was associated with significantly increased risk ($P = 0.02$), whereas consumption of small or moderate quantities of alcohol during pregnancy was associated with significantly reduced risk ($P = 0.03$); it should be noted that no woman consumed during her pregnancy of the index child more than a glass of alcoholic beverages per day. Maternal tobacco smoking and coffee drinking were unrelated to childhood leukaemia risk, even though these exposures were evaluated during the restricted period of the index pregnancy.

None of the environmental exposures in Table 2 was significantly associated with childhood leukaemia risk; in fact diagnostic radiography, ultasonographs and ground floor residence (a proxy for radon exposure) were, if anything, inversely related to this risk.

Among the biomedical variables birthweight was, as expected, positively associated with childhood leukaemia ($P = 0.02$) as was a history of anaemia during pregnancy ($P = 0.003$). None of the other biomedical variables showed a significant association with disease risk, including a history of blood transfusion(s). It is of some interest that hospitalization for allergic diseases was inversely, albeit not significantly, associated with disease risk.

Introduction into the model presented in Table 2 of measures of exposure to magnetic fields from electrical wiring did not substantially affect the results in this table (data not shown).

DISCUSSION

This study, despite including as many cases as have occurred in the country over the study period, is only of moderate size and the use of hospital controls is always a contentious issue. However, the use of hospital controls assured a high level of cooperation from the patients and their guardians, including permission for collection of blood samples. Population-based controls are in principle superior because they represent the study base, but refusal rates can be so high as to compromise the desired comparability between the case and control series (MacMahon and Trichopoulos, 1996). The ability of the present study to show the few established risk factors for childhood leukaemia argues in favour of the validity of other results, and control for socioeconomic status, as reflected in maternal education, should substantially reduce any social class-related selection bias in hospital admission procedures.

Most straightforward were the results of this study in relation to the environmental exposures considered, in that they were convincingly null. Neither the infrequent diagnostic radiography

Table 1 Distribution of 153 childhood leukaemia cases and 300 age-, gender- and residence-matched controls by study variables

Variable	Cases		Controls		*P*-value for trend (direction)
	n	%	*n*	%	
Socioeconomic variables					
Gender					Matched variable
Male	85	55.6	168	56.0	
Female	68	44.4	132	44.0	
Age (years)					Matched variable
≥ 4	71	46.4	124	41.4	
5–9	50	32.7	108	36.0	
≥ 10	32	20.9	68	22.6	
Residence					Matched variable
Urban	82	53.6	173	57.7	
Rural	71	46.4	127	42.3	
Maternal age (years)					0.10 (+)
< 20	11	7.2	21	7.0	
20–24	42	27.5	102	34.0	
25–29	45	29.4	95	31.7	
30–34	40	26.1	61	20.3	
≤ 35	15	9.8	21	7.0	
Maternal education (years)					< 0.001(+)
6–9	51	33.3	157	52.3	
10–12	58	37.9	91	30.3	
> 12	44	28.8	52	17.4	
Sibship size					0.12 (–)
1	29	18.9	56	18.7	
2	99	64.7	166	55.3	
≥ 3	25	16.4	78	26.0	
Birth order					0.11 (–)
1	71	46.4	129	43.0	
2	70	45.8	125	41.7	
≥ 3	12	7.8	46	15.3	
Persons per room					0.05 (–)
< 1.25	15	9.8	16	5.3	
1.25–1.54	39	25.5	68	22.7	
1.55–1.99	62	40.5	126	42.0	
≥ 2	37	24.2	90	30.0	
Day care (ever)					0.81 (+)
No	91	59.5	182	60.7	
Yes	62	40.5	118	39.3	
Lifestyle variables					
Maternal smoking					0.74 (+)
No	76	49.7	154	51.3	
Yes	77	50.3	146	48.7	
Maternal alcohol consumption[a]					0.11 (–)
No	67	43.8	108	36.0	
Yes	86	56.2	192	64.0	
Maternal coffee drinking[b]					0.27 (–)
No	60	39.2	102	34.0	
Yes	93	60.8	198	66.0	
Breast feeding					0.78 (+)
No	52	34.0	106	35.3	
Yes	101	66.0	194	64.7	
Pet ownership[c]					0.06 (+)
No	120	78.4	256	85.3	
Yes	33	21.6	44	14.7	
Environmental variables					
Diagnostic irradiation during pregnancy					0.83 (–)
No	148	96.7	289	96.3	
Yes	5	3.3	11	3.7	
Diagnostic ultrasound during pregnancy					0.94 (+)
No	53	34.6	105	35.0	
Yes	100	65.4	195	65.0	
Residential floor					0.21 (–)
≥ two floors	103	67.3	184	61.3	
< two floors	50	32.7	116	38.7	

Table 1 Cont.

Variable	Cases		Controls		*P*-value for trend (direction)
	n	%	*n*	%	
House heating					0.41 (+)
Non-electrical	113	73.9	232	77.3	
Electrical	40	26.1	68	22.7	
Hair dryer use					0.41 (+)
No	94	61.4	196	65.3	
Yes	59	38.6	104	34.7	
Biomedical variables					
Anaemia during pregnancy					0.01 (+)
No	81	52.9	195	65.0	
Yes	72	47.1	105	35.0	
Diabetes melitus during pregnancy					0.21 (+)
No	150	98.0	298	99.3	
Yes	3	2.0	2	0.7	
Birth weight (g)					0.18 (+)
<2500	4	2.6	19	6.3	
2500–2999	28	18.3	51	17.0	
3000–3499	57	37.3	113	37.7	
3500–3999	45	29.4	93	31.0	
≥ 4000	19	12.4	24	8.0	
Neonatal jaundice					0.80 (+)
No	125	81.7	248	82.7	
Yes	28	18.3	52	17.3	
Blood transfusion(s)[c]					0.83 (–)
No	148	96.7	289	96.3	
Yes	5	3.3	11	3.7	
Allergic disease (hospitalized)					0.04 (–)
No	150	98.0	281	93.7	
Yes	3	2.0	19	6.3	
Total DTP shots[d]					0.36 (+)
0	14	9.1	49	16.3	
1–8	27	17.7	42	14.0	
9–11	37	24.2	51	17.0	
12–13	36	23.5	97	32.4	
≥14	39	25.5	61	20.3	
BCG vaccination					0.76 (+)
No	131	85.6	260	86.7	
Yes	22	14.4	40	13.3	
Total viral vaccination shots[e]					0.09 (+)
0	15	9.8	51	17.0	
1–8	14	9.2	30	10.0	
9–12	35	22.9	65	21.7	
13–15	51	33.3	81	27.0	
≥ 16	38	24.8	73	24.3	

[a]Two or more glasses per week. [b]Three or more cups per week. [c]Ever, before diagnosis. [d]Diphtheria, pertussis, tetanus vaccines; each antigen is counted as a distinct shot. [e]Measles, mumps, rubella, hepatitis B vaccines; each antigen is counted as a distinct shot.

during pregnancy nor the common ultrasound monitoring of pregnancy were related to childhood leukaemia, nor was there evidence that residence at ground level, a proxy for radon exposure, was a risk factor in this data set. Diagnostic irradiation, as currently practised in late pregnancy using modern technology has minimal effect on the risk of childhood leukaemia (Mole, 1990) and the proxy variable for radon exposure used in this study is too crude to capture all but sizable risk elevations (Stjernfeld et al, 1987). Moreover, most studies that have investigated ultrasonography in relation to childhood leukaemia have reported no association. Electrical heating and the use of hair dryers both generate high intensity ELF-magnetic fields, but the associations noted were minimal and far from significant, in accordance with the majority of the evidence on the relationship of such fields to childhood leukaemia (National Radiological Protection Board, 1994; National Research Council, 1996).

Two studies have reported that prenatal exposure to tobacco compounds may increase the risk of childhood leukaemia (John et al, 1991; Cocco et al, 1996), but the results of our study provide little support for this suggestion. Some studies have reported an increased risk for certain subgroups of childhood leukaemia in relation to maternal consumption of alcohol (Severson et al, 1993; Van Duijn et al, 1994), but again our findings are not compatible with this suggestion, again in accordance with the majority of epidemiological evidence (Chow et al, 1996). We do not interpret the statistically significant inverse association of maternal alcohol consumption on childhood leukaemia risk in causal terms; it is far more likely to be a chance phenomenon generated by the multiple comparisons undertaken in the analysis. In agreement with most previous investigations, breast feeding was not significantly associated with disease risk (Hartley et al, 1988, Van Duijn et al, 1988). We also found no evidence that coffee drinking, in the modest

Table 2 Multiple logistic regression-derived, mutually adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) for childhood leukaemia in relation to specified exposures

Variable	Category or increment	OR	95% CI	*P*-value
Sociodemographic variables				
Maternal age at birth	5 years	1.19	0.93–1.52	0.17
Maternal education	~4 years	1.48	1.17–1.87	0.001
Sibship size	one	1.40	0.88–2.23	0.16
Birth order	one	0.74	0.48–1.15	0.18
Persons per room	~0.4	0.83	0.63–1.11	0.21
Day care	ever (vs never)	0.83	0.51–1.37	0.46
Lifestyle variables				
Maternal smoking	yes (vs no)	1.19	0.73–1.93	0.49
Maternal alcohol consumption[a]	yes (vs no)	0.57	0.34–0.95	0.03
Maternal coffee drinking[b]	yes (vs no)	0.89	0.55–1.46	0.65
Breast feeding	yes (vs no)	0.85	0.52–1.41	0.54
Pet ownership[c]	yes (vs no)	2.18	1.14–4.16	0.02
Environmental variables				
Pregnancy radiography	yes (vs no)	0.84	0.25–2.78	0.77
Pregnancy ultrasound	yes (vs no)	0.74	0.41–1.32	0.30
Residential floor	ground level (vs other)	0.85	0.50–1.43	0.53
House heating	electrical (vs non-electrical)	1.04	0.60–1.79	0.89
Hair dryer use	yes (vs no)	1.37	0.79–2.37	0.27
Biomedical variables				
Anaemia during pregnancy	yes (vs no)	2.60	1.39–4.86	0.003
Diabetes melitus during pregnancy	yes (vs no)	2.99	0.30–29.56	0.35
Birthweight	500 g	1.36	1.04–1.77	0.02
Neonatal jaundice	yes (vs no)	1.44	0.74–2.78	0.28
Blood transfusions(s)[c]	yes (vs no)	0.22	0.38–4.93	0.64
Allergic disease (hospitalized)	yes (vs no)	0.36	0.09–1.43	0.15
Total DTP shots[d]	~3	0.97	0.71–1.32	0.83
BCG vaccination	yes (vs no)	1.44	0.66–3.13	0.36
Total viral vaccination shots[e]	~3	1.23	0.91–1.66	0.16

[a]Two or more glasses per week. [b]Three or more cups per week. [c]Ever, before diagnosis. [d]Diphtheria, pertusis, tetanus vaccines: each antigen is counted as a distinct shot. [e]Measles, mumps, rubella, hepatitis B vaccines: each antigen is counted as a distinct shot.

quantities usually consumed during pregnancy in Greece, affects childhood leukaemia risk.

Pet ownership is not considered among the lay public in Greece as a possible risk factor for childhood leukaemia nor was the hypothesis considered as credible by the investigators during the planning and implementation of the study; it is therefore unlikely that information bias is responsible for the statistically significant positive association, although chance is again a possible explanation. It is worth noting, however, that ownership of a cat, a common domestic animal in Greece, has also been implicated in the aetiology of childhood leukaemia in earlier investigations (Bross and Gibson, 1970; Buckley et al, 1994).

Among the sociodemographic variables investigated none emerged as a powerful or statistically significant risk predictor, with the exception of a higher standard of maternal education, the most reliable indicator of socioeconomic status in Greece (Trichopoulos, 1982). Many studies have supported a link of childhood leukaemia with higher socioeconomic status in several populations through use of different social class indicators (Greenberg and Shuster, 1985; Van Steensel-Moll et al, 1986; Kaye et al, 1991). The positive association of maternal age at birth with disease risk, although not statistically significant, is compatible with the results of most earlier investigations that addressed this issue, (MacMahon and Newill, 1962; Buckley et al, 1994; Chow et al, 1996); null results, however, have also been reported from several major investigations (Robison et al, 1987; Zack et al, 1991).

The inverse associations of birth order, household crowding and day care attendance with childhood leukaemia risk are statistically non-significant but they all point to a higher risk of the disease with delayed exposure to infectious agents. These findings are consistent with the infection hypotheses of childhood leukaemia proposed by Kinlen et al (1990), Greaves and Alexander (1993) and other investigators (Van Steensel et al, 1986; MacMahon, 1992; Petridou et al, 1993; Kinlen, 1995; Kinlen et al, 1995). Our limited data on blood transfusion do not support a blood-transmitted agent being responsible for childhood leukaemia, in keeping with the larger study of Memon and Doll (1994). We have found no evidence that BCG and DTP vaccinations or immunization against common viral childhood infections conveyed protection, in spite of some previous reports (Haro, 1986; Kneale et al, 1986; Hartley et al, 1988; Nishi and Miyake, 1989). In fact, our data, if anything, indicate the opposite. The inverse association with allergic diseases is statistically non-significant and could be due to chance, but it deserves some attention in view of the fact that inverse associations have also been reported for other forms of cancer (Jain et al, 1991; Bueno et al, 1992).

The positive association between birth weight and the risk for childhood leukaemia has been reported by many investigators

(MacMahon and Newill, 1962; Fasal et al, 1971; Hirayama, 1980; Daling, 1984; Robison et al, 1987) and, notwithstanding a few null reports, the association appears to be genuine. The credibility of this association is supported by the plausible, albeit weak, leukaemogenic effect of growth hormone and the reported link between height and acute lymphoblastic leukaemia (Broomhall et al, 1983). Additional evidence in support of an association between some growth processes and risk of childhood leukaemia can be found in two other results of the present investigation: the positive association with anaemia during pregnancy, because anaemia is associated with increased placental weight (Godfrey et al, 1991), and the non-significant, positive association with diabetes mellitus during pregnancy, because of the intimate link of diabetes mellitus with IGF1 and growth in general. The non-significant association with neonatal jaundice in our data could be due to chance, but a similar association has been reported from an American investigation (Buckley et al, 1994) and a Swedish study (Zack et al, 1991). The pathophysiology of neonatal jaundice is not fully understood but a link with oestrogens that have growth-promoting potential has been suggested (Lauritzen et al, 1966; Robine et al, 1988).

It is not easy to integrate the results of this investigation into a coherent pattern when taking into account the collective evidence from earlier investigations. Nevertheless, our data appear to be compatible with acute childhood leukaemia being linked with a delayed development of herd immunity to fairly common infectious agents, in conjunction with accelerated perinatal and early post-natal growth. This hypothesis could explain the positive associations with maternal education, birth weight and anaemia during pregnancy, as well as the inverse associations with birth order, household crowding and day care attendance. The multitude and unpredictability of factors that shape herd immunity and determine growth could explain why the odds ratio for each of these factors deviates only modestly from the null value. Pet ownership may be important only in particular settings, depending on epizootic parameters, but the issue deserves more attention. The modest size of the present study did not allow investigation of acute childhood leukaemia by histological subtype, but the risk factor profile that is indicated is clearly heavily weighted by the dominant type of acute lymphoblastic leukaemia.

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