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RESEARCH

Investigating the Relationship between Mortality from Respiratory Diseases and Childhood Acute Lymphoblastic Leukaemia in Hungary

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Abstract Our aim was to investigate the ecological association between death from infectious disease of the respiratory system and the risk of acute lymphoid leukaemia (ALL) in children aged less than 7 years. Poisson regression analyses were carried out using overall data and gender-specific models. The study included 176 cases (92(52.3 %) boys and 84 (47.7 %) girls) of ALL in those aged 0–6 years in South Hungary. Eight cases were diagnosed before the age of 1 year. A significant risk of ALL disease was observed with higher levels of mortality from the chronic respiratory diseases (p=0.035) and pneumonia (p=0.010) among children aged 2–5 years (Odds Ratio for trend was 1.001 and 95%CI [1.000–1.002] and Odds ratio for trend was 1.013 and 95%CI [1.003–1.023], respectively). Significantly increased risk of childhood ALL was detected among children under 1 year of age residing in areas around birth with higher levels of mortality from influenza (Odds Ratio (OR) for trend was 1.05; 95%CI [1.01–1.09]; p=0.012). This risk was also detected in girls (p<0.001), but not in boys (p=0.43). Our findings provide new evidence that will help to understand the different pattern of female and male childhood ALL occurrence , but further studies are needed using detailed individual medical history to clarify the role of influenza and other infectious diseases in the etiology of childhood ALL and to explain gender-specific effects.

Keywords Childhood acute lymphoblastic leukaemia · Gender-specific difference · Deaths from respiratory infections · Poisson regression

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Introduction

A number of previous epidemiologic studies have suggested that infectious disease may be involved in the etiology of childhood leukemia [1, 2]. Acute lymphoid leukaemia (ALL) is the most common type of cancer found in children and exposure to infections before or around birth may be associated with the risk of childhood ALL, but the findings are contradictory [2].

Hakulinen and colleagues reported a statistically significant association between maternal influenza of the 1957 “Asian” type and subsequent later leukaemia in the infants [3]. Bithell and colleagues also found a significant association between influenza virus infections during pregnancy and subsequent leukaemia disease in the child using retrospective data from the Oxford Survey of Childhood Cancers [4]. However, Randolph and colleagues and Curnen and colleagues found no association between maternal influenza infection and childhood leukaemia [5, 6]. Furthermore, Kwan and colleagues

reported an increased risk of ALL in offspring of mothers infected by influenza [7].

A few studies described the relationship between infectious agents (measles, chicken pox or scarlet) and childhood malignancies but the findings were also contradictory. While Parodi and colleagues described an inverse association between the occurrence of childhood diseases (measles, rubella, chickenpox, mumps, pertussis and scarlet fever) and the risk of leukemia and non-Hodgkin's lymphoma [8], Nyari and colleagues found no association [9]. Our aim was to investigate the ecological relationship between death from infectious disease of the respiratory system and the risk ALL in children aged under 7 years using high quality population-based data from Southern Hungary.

Methods

Study Population and Cases

The area considered is South Hungary which includes two regions—South Transdanubia and South Great Plain (Fig. 1). Children born during 1981–2000 were considered.

Registrations of first malignancies for children, born in South Hungary and diagnosed under age of 7 years in Hungary before the end of 2008 were obtained from the Szeged and Pécs centres of the Hungarian Paediatric Oncology Group (HPOG). Population-based registration of leukaemia was initiated in 1971. Regularly updated patient files are available in both regions and the national registry. Thus, ascertainment is considered to be complete for the time period of 1981–2000. The residential place with postcode at diagnosis of each ALL cases were assigned to one of six county districts within the study area.

The gender, year and county district of birth of all live birth registrations in the study period were obtained from the Central Demographic Agency [10]. Hence the numbers of male and female births in each county district in each year were calculated.

Numbers of annual deaths were available by county districts in Hungary. Deaths from influenza (ICD9: 487, ICD010: J10-J11), deaths from chronic bronchitis (ID9: 490–496, ICD10 J41-J42) and deaths from pneumonia (ID9: 480–486, ICD10 J12-J18)) were considered as exposures. From published statistics on infectious deaths [10], data were abstracted on: annual total number of cases of deaths from respiratory diseases, including influenza by county districts, hence the numbers of male and female deaths from respiratory diseases, including influenza in each county district in each year were calculated.

Poisson regression was used to investigate the relationship between risk of cancer and measures of community infections (e.g.: number of deaths in respiratory diseases, which includes flu). Analyses were carried out at county district level using overall data and gender-specific models. The ALL cases were aggregated into the following age groups: age 0–6 years, age under 1 year old, age between 1 and 5 years, age between 2 and 5 years (the childhood ALL peak range) which were used

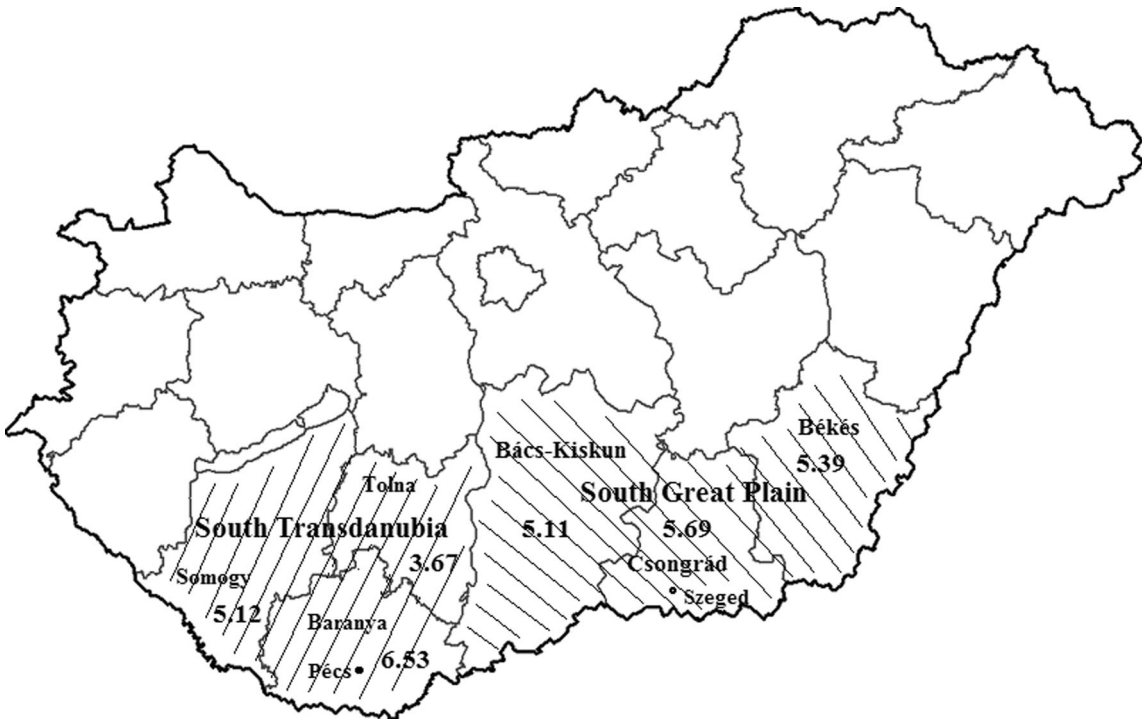

Fig. 1 The incidence rate of ALL per 100,000 person years people in South Hungary

in the analyses. Nevertheless, age between 1 and 6 years and age between 2 and 6 years were used for sensitivity analyses. Furthermore, sensitivity analyses were carried out to test the models using the period of time used in our previous studies between 1981 and 1998 [11–13]. A p-value less than 0.05 was considered significant. All analyses were performed with STATA Software version 8.0 (StataCorp LP, College Station, TX , USA).

Results

The total numbers of deaths during the 20-year period were 26,753, 5,649 and 770 from chronic bronchitis, pneumonia and influenza, respectively. The median chronic respiratory diseases, pneumonia and influenza mortality rate was 815.8 per 100,000 persons per year with an inter quartile range (IQR) of [511.5–1280.1] per 100,000 persons per year, 176.1 per 100,000 persons per year with IQR of [144.0–232.6] per 100,000 persons per year and 22.6 per 100,000 persons per year with an inter quartile range (IQR) of [18.5–37.7] per 100,000 persons per year, respectively.

The study included 176 cases (92 (52.3 %) boys and 84 (47.7 %) girls) of ALL in those aged 0–6 years in South Hungary. Eight cases (six boys and three girls) were diagnosed before the age of 1 year. There were 547,034 live births in the study area during the 20 year-interval of 1981–2000. The overall incidence rate of ALL was 5.37 per 100,000 persons per year for children aged 0–6 years. The peak ages of diagnosis of childhood ALL was between 2 and 5 years (Table 1.).

A significant risk of childhood ALL was observed with higher levels of mortality from chronic respiratory disease (bronchiolitis, pneumonia and influenza) among children aged 2–5 years (p=0.035) and 2–6 years (p=0.033). Similar significant trend was found between the risk of ALL and mortality from pneumonia at peak age groups aged 2–5 years (p=0.010) and aged 2–6 years (p=0.025) (Table 2). However, in the gender-specific analyses these trends were almost significant in girls (p=0.08), but not in boys (Table 3).

Nevertheless, significantly increased risk of childhood ALL was detected among children under 1 year of age residing in areas around birth with higher levels of mortality from influenza (OR for trend was 1.05; 95%CI [1.01–1.10]; p=0.012). This increased risk was detected in girls (OR:1.22 95%CI [1.05–1.42]; p=0.009), but not in boys (OR=0.91 95 % CI [0.65–1.26]; p=0.56]) .

In the sensitivity analyses the period of time between 1981 and 1998 was used, where significant risk of ALL was found among children aged 2–5 years residing in areas around birth with higher levels of mortality from pneumonia: OR: 1.013 95%CI [1.000–1.026]; p=0.049 and almost significant from the chronic respiratory diseases :OR for trend 1.001, 95%CI

Table 1 The distribution of childhood ALL overall and in boys and girls in different age groups

	Boys	Girls	Total
Age under 1 year	5	3	8
1 year ≤ age<2 years	11	8	19
2 year ≤ age<3 years	15	19	34
3 year ≤ age<4 years	23	17	40
4 year ≤ age<5 years	21	19	40
5 year ≤ age<6 years	10	8	18
6 year ≤ age<7 years	7	10	17
Total	92	84	176

Table 2 The risk estimate of childhood ALL among children residing in areas around birth with higher levels of mortality from the chronic respiratory diseases and pneumonia (odds ratio (OR) for trend and 95 % confidence interval (95%CI)

Mortality from	Age at ALL diagnose	OR	95 % Confidence Interval		P–value
			Lower	Upper	
Chronic respiratory diseases	0–6 years	1.001	0.998	1.002	0.122
	2–5 years	1.002	1.0001	1.003	0.035
	2–6 year	1.002	1.0001	1.003	0.033
Pneumonia	0–6 years	1.005	0.997	1.013	0.195
	2–5 years	1.013	1.003	1.023	0.010
	2–6 years	1.019	1.001	1.020	0.025

Table 3 The gender-specific risk estimate of childhood ALL among children residing in areas around birth with higher levels of mortality from the chronic respiratory diseases and pneumonia (odds ratio (OR) for trend and 95 % confidence interval (95%CI)

Mortality from	Age at ALL diagnose	OR	95 % CI		P–value
			Lower	Upper	
Boys					
Chronic respiratory diseases	0–6 years	1.002	0.998	1.005	0.312
	2–5 years	1.002	0.998	1.006	0.276
	2–6 year	1.002	0.998	1.006	0.194
Pneumonia	0–6 years	0.996	0.989	1.002	0.210
	2–5 years	1.000	0.997	1.002	0.954
	2–6 years	1.000	0.997	1.002	0.931
Girls					
Chronic respiratory diseases	0–6 years	1.004	0.998	1.006	0.327
	2–5 years	1.004	0.999	1.008	0.080
	2–6 years	1.003	0.998	1.007	0.174
Pneumonia	0–6 years	1.005	0.990	1.027	0.362
	2–5 years	1.018	0.999	1.036	0.073
	2–6 years	1.013	0.994	1.036	0.166

[1.000–1.003]; p=0.08. Moreover, the risk of childhood ALL among children under 1 year of age residing in areas around birth with higher levels of mortality from influenza was also detected : OR for trend was 1.06; 95%CI [1.01–1.12]; p=0.017. Similarly, increased risk was detected in girls (OR: 1.20 95%CI[1.03–1.41]; p=0.023), but not in boys (OR=0.96 95%CI[0.74–1.27]; p=0.80).

Discussion

Our study included a large sample of a population over a 20-year period of time. The two South-Hungarian regional registries covers nearly a quarter of the childhood population of the country providing a representative sample of Hungarian children. We focused on this age group because it includes the peak incidence [14]. Thus, in our study the peak of childhood leukemia cases diagnosed under 7 year was selected to analyze infectious effects on developing ALL.

A significant risk of ALL was detected with higher levels of mortality from the chronic respiratory disease and pneumonia among children aged 2–5 years. However, in the gender-specific analyses these trends remained significant in girls, but not in boys. Furthermore, we found significant risk of ALL among children aged under 1 year. This risk was more marked in girls but was not in boys which may explain the gender-specific difference in developing ALL in children. In spite of the apparent limitation of our study that we have not had data on other infectious agents, including measles, chicken pox, and adenovirus and the numbers of death in respiratory diseases which includes influenza were considered as exposures. Thus, this 20-year long study supports new evidence that helps the understanding of different pattern of female and male childhood ALL cases. To avoid a misinterpretation of a chance finding, sensitivity analyses were carried out. The results of the sensitivity analyses confirmed the main findings. Moreover, the incidence of ALL corresponds to that reported by others [15, 16].

In an earlier study different seasonal variation in boys and girls were found in South Hungary where the peaks were in February and in November, respectively [11]. Also different risk was detected in a study of population mixing, where in a gender-specific analysis the higher level of population mixing increased the risk of ALL in boys only [12]. In a recent study, we found different clustering patterns between female and male cases [13].

This model was applied in an earlier study of children born in the county of Cumbria, north-west England to investigate whether levels of infection in the community around the time of birth were associated with the risk of developing cancer, and no association was found between the risk of leukaemia and measures of community infections (measles, respiratory and other infections) [9].

Kroll and colleagues reported incidence time trends for childhood leukaemia in Britain during 1974–2000 and suggested that small peaks in incidence may be associated with influenza epidemics [17]. In contrast, Shore and colleagues [18] and Dockerty and colleagues [19] found no relationship between influenza incidence and childhood leukaemia.

More follow-up studies are needed where detailed maternal, perinatal, infant and childhood medical history data are collected and analysed to enhance understanding of the role that infections, including influenza, may play in the aetiology of childhood ALL and to explain gender-specific effects.

Declaration of Interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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