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RESEARCH

Spatial Clustering of Childhood Acute Lymphoblastic Leukaemia in Hungary

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Abstract The aetiology of childhood acute lymphoblastic leukaemia has been linked with spatially heterogeneous environmental exposures. The presence of spatial clustering would be consistent with geographically localized environmental exposures over long periods of time. The present study is the first to examine spatial clustering amongst children aged 0–4 years using population-based data from Hungary. The data set consisted of 134 children diagnosed with acute lymphoblastic leukaemia who were resident in part of Hungary during the period 1981–2000. Two levels of spatial aggregation were examined: counties and settlements. The Potthoff-Whittinghill and Moran I autocorrelation methods were used to test for spatial clustering. Additionally, an evaluation of the environmental changes during the study period was considered. Specifically analyses were carried out on sub-periods to investigate a possible effect of the Chernobyl catastrophe. There was statistically significant spatial clustering both at the county (estimate of extra-Poisson variation $\left(\widehat{\beta}\right) = 0.56$, P=0.04) and settlement levels (estimate of extra-Poisson variation $\left(\widehat{\beta}\right) = 0.68$, P=0.0003). At county level, the finding was attributable to clustering amongst female cases, but at settlement level, the finding was limited to male cases. There was significant spatial autocorrelation in the sub-periods immediately following the accident (1986–1990 & 1991–1995), but not before 1986, nor after 1995. A significant autocorrelation was observed during the 5 year period immediately following the accident (1986–1990, global Moran I=0.1334, p=0.005). The centre of significant excesses of ALL cases was located in the county of Baranya. Our study is consistent with an environmental aetiology for acute lymphoblastic leukaemia in children associated with constant exposure to an, as yet unknown, environmental factor in small geographical areas. Although a possible effect of the Chernobyl accident was found in the autocorrelation analysis, the role of chance cannot be excluded.

Keywords Acute lymphoblastic leukaemia · Aetiology · Childhood · Cluster analysis · Environmental exposure · Spatial distribution · Gender specific effect · Male predominance

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Introduction

Acute lymphoid leukaemia (ALL) is the most common type of cancer found in children. Infection has long been suspected as a possible factor in the aetiology of ALL. Early reports suggest a significant association between childhood leukaemia and maternal viral infections during pregnancy

[1]. Recent epidemiological studies have suggested that exposure to infections before or around birth may be associated with the risk of ALL in children [1, 2].

Some of the environmental exposures that have been putatively linked to aetiology may exhibit geographical variation. These include ionizing radiation, electromagnetic fields, chemical exposures, contaminated drinking water and infections. If any of these exposures do play a role in aetiology then the distribution of cases of childhood leukaemia may be predicted to exhibit spatial heterogeneity. A number of previous studies from parts of Europe, Australia, New Zealand and Hong Kong have found statistically significant spatial clustering amongst cases of childhood leukaemia [3–6]. However, studies from North West England, Germany, France and Sweden showed no evidence of spatial clustering for childhood leukaemia [7–10].

The aim of our study was to investigate the presence of spatial clustering that might arise as a result of persistent and localized environmental exposures using an independent population. The study is the first spatial clustering analysis of childhood leukaemia from Hungary.

Patients and Methods

Study Participants

The area considered was South Hungary which includes two regions—South Transdanubia and South Great Plain. Children born between 1981 and 2000 were considered. Births and cases were assigned to six county districts within the study area.

Registrations of first malignancies for children, born and diagnosed under age 5 years in Hungary before the end of 2005 were obtained from the Hungarian Paediatric Oncology Group (HPOG). The ALL registrations were based on address of residence of the family. Annual data on population of each settlement by gender in the study period were obtained from the Central Demographic Agency.

Statistical Methods

The Potthoff-Whittinghill (PW) and Moran I methods were used to test for spatial clustering and autocorrelation, respectively [11, 12]. The PW method requires age structured aggregated case and population data for small geographical areas. Analyses were performed at two levels of areal resolution, counties and settlements. There were 6 counties with population sizes ranging from 233,650 to 528,418 and area in square kilometer ranging from 3,703.31 to 8,445.15. There were 906 settlements with population sizes ranging from 73 to 158,158 and area in square kilometer ranging from 4.96 to 280.84.

The parameter for assessing the magnitude of the spatial clustering is extra-Poisson variation (EPV). The estimate for EPV would equal zero if there was no spatial clustering and would be greater than zero if there was spatial clustering.

The spatial distribution of cases in the study area was simulated. For each small area the number of cases was assumed to have an independent Poisson distribution, with mean equal to expectation. For all analyses a total of 10,000 simulations were performed conditional on the total number of cases being fixed. For each simulation a value of the PW statistic was obtained and thus the distribution of the test statistic was estimated. The observed value of the PW statistic, PW_O, was then compared with the simulated values, PW_S (where S=1,…..,10,000). One-sided P-values were estimated by calculating the proportion of the total number of simulations for which $PW_S > PW_O$. Statistical significance was taken as $P<0.05$ in all analyses.

Similarly, the spatial distribution of cases in the study area was simulated to measure spatial autocorrelation index between the incidence rates in the geographical units using Moran I method.

Additionally, an evaluation of the environmental changes during the study period was considered. Specifically, subperiod analyses were carried out to investigate the possible effect of the Chernobyl catastrophe (which happened in April 1986). Therefore, the study period was divided into 5 years intervals as 1981–1985, 1986–1990, 1991–1995 and 1996–2000.

Results

The study included 134 cases (73(54.5 %) boys and 61 (45.5 %) girls) of ALL in those aged 0–4 years in South Hungary (Table 1). Eight cases (five 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 4.90 per 100,000 person years for children aged 0–4 years. The highest incidence rates of 6.79 per 100,000 person years and 6.41 per 100,000

Table 1 Population and patient breakdown of ALL cases between 1981 and 1997 in South Hungary

Age	Girls	Boys	All Children
<1 year	3	5	8
1 year	9	14	23
2 years	19	13	32
3 years	15	22	37
4 years	15	19	34
Total	61	73	134

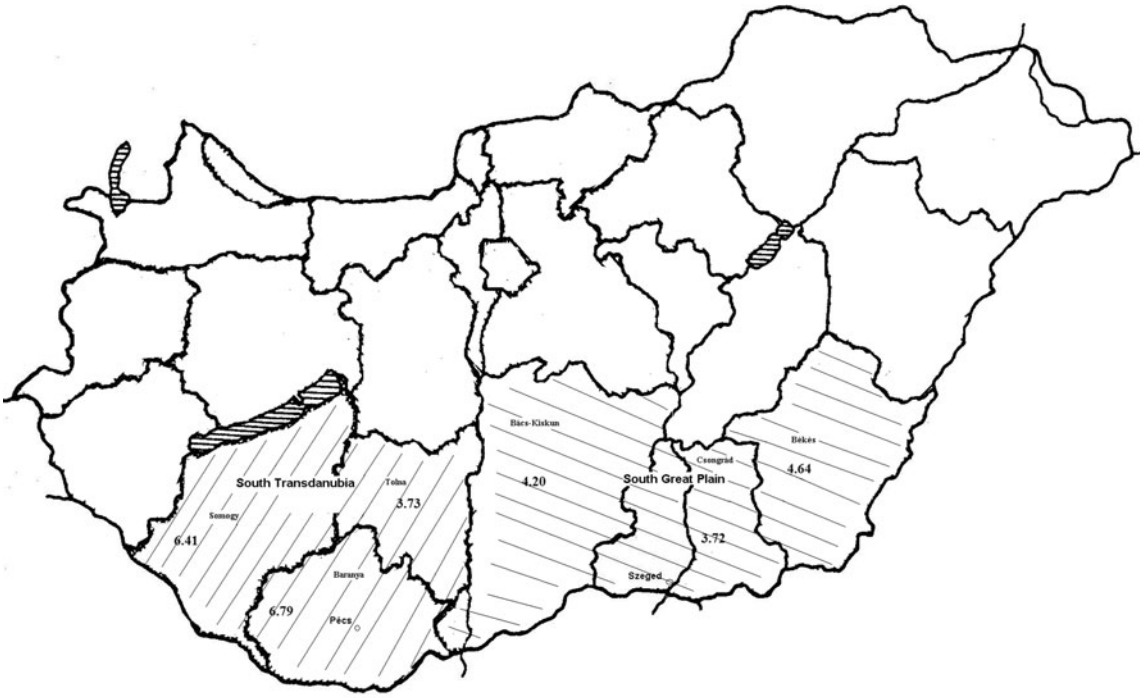

Fig. 1 The incidence rate of ALL per 100,000 person years people in South Hungary

person years were found in western counties of South Hungary (Fig. 1).

The demographic characteristic of the population and incidence rates of ALL are summarized in Table 2. The incidence rate of boys (5.21 per 100,000 person years) were non-significantly higher than the incidence rate of girls (4.57 per 100,000 person years). The female incidence rates varied from 2.81 to 5.27 per 100,000 person years, and the male incidence rates varied from 3.63 to 8.30 per 100,000 person years between counties.

Table 3 shows a statistically significant spatial clustering for all cases within smaller settlements which was attributable to clustering of male cases. The cumulative incidence rates of male ALL cases per 5,000 people in South Hungary are shown in Fig. 2. The highest observed incidence rates of ALL at settlement level were 6.29 and 5.38 per 1,000 persons in Baranya and Somogy counties between 1996 and2000, respectively.

A significant spatial autocorrelation was found in the incidence of ALL for all cases in the Moran analysis (I=0.18, p=0.0012) over the whole period. The global Moran (I=0.14) statistic was significant (p=0.028) among boys, but non-significant among girls (I=0.04, p=0.16). Since the study period includes the time of the Chernobyl accident (in April 1986), we analyzed the effect of the catastrophe. There was no significant autocorrelation in the unexposed period 1981–1985, before the accident. However, a significant autocorrelation was observed during the 5 year period immediately following the accident (1986–1990, global Moran I=0.1334, p=0.005). The centre of significant excesses of ALL cases was located in the county of Baranya according to the local Moran I statistics. Further, significant autocorrelation was found during the period 1991–1995 (global Moran I=0.0.054, p=0.018). In contrast, no autocorrelation was observed after 1995. Finally, a gender

Table 2 Number of ALL cases, births (1981–2000), and incidence (per 100,000 person years) of ALL, among boys and girls born in Southern Hungary

County		Number of births	Number of ALL cases	Incidence
Boys				
	Bács-Kiskun	65,546	12	3.66
	Baranya	48,198	20	8.30
	Békés	46,116	10	4.33
	Csongrád	49,642	9	3.63
	Somogy	40,132	15	7.47
	Tolna	30,453	7	4.60
	Total	280,087	73	5.21
Girls				
	Bács-Kiskun	63,061	15	4.76
	Baranya	46,094	12	5.21
	Békés	44,378	11	4.96
	Csongrád	47,018	9	3.83
	Somogy	37,927	10	5.27
	Tolna	28,469	4	2.81
	Total	266,947	61	4.57

Table 3 Results of spatial clustering analyses using Potthoff-Whittinghill method

Group	EPV ($\widehat{\beta}$)	*P*-value
Settlements		
Males	$\widehat{\beta} = 0.22$	*P*=0.003
Females	$\widehat{\beta} = 0.07$	*P*=0.20
Total cases	$\widehat{\beta} = 0.68$	*P*=0.0003
Counties		
Males	$\widehat{\beta} = 0.02$	*P*=0.39
Females	$\widehat{\beta} = 0.38$	*P*=0.08
Total cases	$\widehat{\beta} = 0.56$	*P*=0.04

difference was not found in the 5 year periods that were investigated in the autocorrelation analysis.

Discussion

Main Findings

In this study, significant spatial clustering for all cases at the smaller settlement level was found which was attributable to clustering of male cases. This finding partly confirms our previous results where different pattern of risk to acute lymphoid leukaemia was found in boys and girls aged under 5 years [13, 14] and was attributable to an association between the risk of childhood leukaemia and population mixing, which has been interpreted as evidence of an infectious aetiology. Nevertheless, a possible effect of the Chernobyl catastrophe was observed in the autocorrelation analyses in the incidence of childhood ALL during the 10 years following the time of the accident.

Strengths and Weaknesses of Study

South Hungary, the area considered, covers nearly a quarter of the childhood population of the country providing a representative sample of Hungarian children. Thus, our study included a large sample of a population over a 20 year period of time.

It is important to note that the spatial clustering found amongst children could have arisen by chance or it could be explained by lifestyle factors, characteristics of the residential area or another unmeasured heterogeneous geographical factor. However, the applied clustering analyses have used an optimal statistical method for detecting the global occurrence of localized aggregations of cases.

As far as we are aware, this is the first epidemiological study reporting the effect of spatial clustering of ALL for boys and girls separately.

Comparison with Other Studies

The peak of childhood leukemia occurs under 5 years [15]. Smith suggested that childhood peak ALL is due to in utero exposure to infection. This childhood peak mainly consists

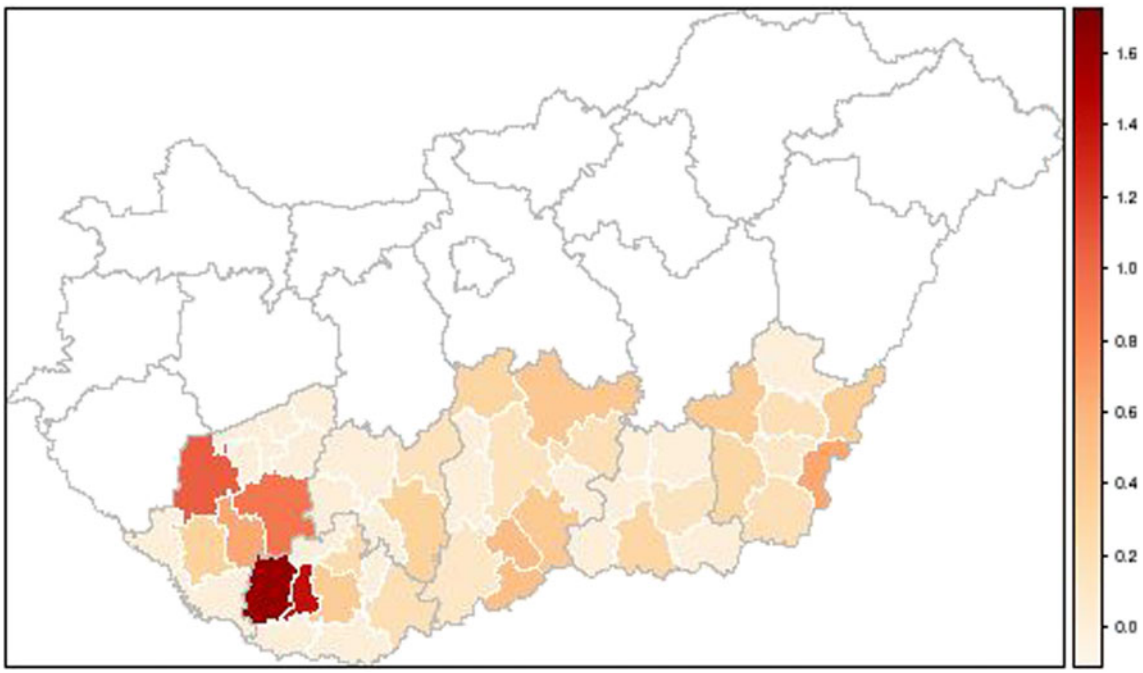

Fig. 2 The cumulative incidence rate of boys diagnosed with ALL per 5,000 people in South Hungary

of cases of precursor B-cell ALL [1, 16]. We applied spatial clustering and Moran's autocorrelation methods to investigate the role of environmental effects in the development of ALL since these methods could be applied if an aetiologically linked environmental exposure is present in localised high-risk small areas, but is absent in low-risk areas [17, 18]. A number of statistical methods have been developed to test for spatial clustering. Alexander and Boyle [17] evaluated the empirical performance of a number of methods for detecting spatial clustering. These included methods due to Black et al. [18], Potthoff and Whittinghill [11, 12], Cuzick and Edwards [19], Openshaw [20], Besag and Newell [21], Diggle and Chetwynd [22], Anderson and Titterington [23], and Oliver et al. [24]. Fifty simulated data sets were created to reflect a range of feasible clustering scenarios. Overall, the Potthoff and Whittinghill method [11] was shown to be consistently the most powerful method for detecting spatial clustering [17]. Additionally, Moran's I method was applied to test autocorrelation [12].

Similarly to Bellec et al. [10], a significant spatial autocorrelation in the incidence of childhood ALL (Moran's I=0.18, p<0.0012) was found over the whole study period 1981–2000. However, they did not find evidence for the existence of a spatial heterogeneity in the incidence of childhood acute leukaemia in France using the Potthoff and Whittinghill method.

The present study concerns 'spatial clustering', which is the detection of an irregular geographic spatial distribution of cases that is not confined to one particular small area or restricted time period. This type of clustering could arise when there are a small number of areas with greatly increased incidence or a large number of areas with moderately increased incidence over long periods of time. Spatial clustering could arise if an aetiologically linked environmental exposure is present in localised high-risk small areas, but is absent in low-risk areas. Spatial clustering is likely to occur in the presence of an environmental exposure which persists over a long period of time [18–20]. In this study, we investigated the spatial clustering of ALL in South Hungary over a period of 20 years.

The clustering analyses have used an optimal statistical method for detecting the global occurrence of localized aggregations of cases [21], a test which performs well especially when a large number of clusters are present [22–25].

Spatial clustering could not determine the type of environmental factor involved. Further studies are needed to investigate the effect of a possible infectious etiology as contradictory findings have been reported. Hakulinen et al. [26] described a relationship between an epidemic of flu and childhood leukemia in Finland. However, Nyári et al. found no evidence in a study from the Northern England region [27].

Török et al. found a significant increase in incidence of ALL in Hungary after the Chernobyl accident [28]. Dickinson and Parker [29] reported an association between paternal preconcepcional irradiation and childhood leukemia. In the present study, significant autocorrelation was detected after the Chernobyl catastrophe in the incidence of childhood ALL during the following 10 years after the accident compared to the 5 year unexposed study period. However, this could be a chance finding as spatial clustering analysis detects the persisting environmental exposure over a long period. Therefore, we are planning to carry out further investigations of the infectious origin to investigate other factors (e.g. the effect of socio-economical status).

In summary, we have used a rigorous statistical method and high-quality data from a population-based register of childhood leukaemia. This is the first analysis to identify spatial clustering of childhood ALL in Hungary. Our findings confirm the previously reported results where different patterns of risk to ALL were found in boys and girls aged under 5 years. Although, a significant autocorrelation was found after the Chernobyl catastrophe in the incidence of childhood ALL this, however, could be a chance finding. In conclusion, further research is required to understand better the precise nature of these geographical differences in Hungary.

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