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ORIGINAL PAPER

# Seasonal Variation of Childhood Acute Lymphoblastic Leukaemia is Different Between Girls and Boys

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**Abstract** The aim of this study was to investigate seasonal trends in the incidence of acute lymphoblastic leukaemia (ALL) around the times of birth and diagnosis in children aged 0–4 years and also to examine gender specific effects. Children born in South Hungary during 1981–1997 were analysed. Registrations of first malignancies for children, diagnosed under age 5 years before the end of 2002 were obtained from the Hungarian Paediatric Oncology Group providing a representative sample of Hungarian children over a 17 year period of time. Data were available on the corresponding numbers of births for each month of the study period were obtained. Statistical analyses were performed using logistic regression with harmonic components. The study analysed 121 cases of children, aged under 5 years, who were diagnosed with ALL. We found no seasonal effect related to date of diagnosis. However, there was seasonal variability for ALL related to date of birth. Maximal rates were seen in children born in February and August in the simple harmonic regression model for all children diagnosed with ALL. Analysis by gender found evidence of seasonality related to month of birth with peaks in February and August in boys, but different seasonal effects were seen for girls (peak in November, nadir in May). Our study provides some evidence that male specific immune responses to infections around the time of birth could explain the male predominance in the incidence of ALL.

**Keywords** Childhood acute lymphoblastic leukaemia · Gender specific seasonal effect · Male predominance · Simple harmonic regression

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## Introduction

Environmental hazards including infections have long been suspected as a possible factor in the aetiology of leukaemia and lymphoma (ALL) [1–3]. If seasonal variation in the onset of disease could be shown in any of the diagnostic subgroups of leukaemia or lymphoma, this could be interpreted as supportive evidence of an aetiology linked to exposure to infection [4, 5].

In a previous study [6] we reported the relation between population mixing around the time of birth and the subsequent risk of acute lymphoblastic leukaemia (ALL) in children under 5 years of age. In the sex specific models there was significant association between population mixing and risk of ALL in boys, however, the relationship

between population mixing and risk of ALL for girls was less marked and not significant.

The aim of this study was to investigate, in a different geographical area from previous studies, seasonal trends of ALL around the time of birth and date of diagnosis in all children aged 0–4 years and also for boys and girls separately.

## Methods

### Study Population

The study area was South Hungary which includes two regions—South Transdanubia and South Great Plain. Children born during 1981–1997 were analysed. Registrations of first malignancies for children, born and diagnosed under age 5 years in Hungary before the end of 2002 were obtained from the Hungarian Paediatric Oncology Group [7].

The Central Demographic Agency [8] provided data on the number of births for each month over the study period but by gender only for each year. The number of births in each month for each gender was estimated assuming no monthly variation in the gender ratio within any year.

### Statistical Methods

The logistic regression model including periodic functions (a sine and a cosine function, simultaneously) was applied for the detection of seasonal variations. This method was described by Stolwijk et al. [9] in detail previously. Monthly, two monthly and two weekly time units were used to analyse the data. The pattern of annual cyclical variation was studied using dates of both birth and first diagnosis with ALL. The magnitude of the seasonal variation, as expressed by the amplitude of a simple harmonic oscillation, was also calculated. The time at which the maximum and minimum incidences occurred was estimated using single and double peaks within the period of year. The $\chi^2$ goodness-of-fit test was used to examine the adequacy of the description of the data by a harmonic curve. Analyses were conducted for all cases and for boys and girls separately. All analyses were performed using STATA Software (version 8.0).

## Results

The total number of childhood ALL cases in South Hungary identified for the study was 121 (63 (52%) boys and 58 (48%) girls) diagnosed under age 5 years. There were 481,984 live births in the study area, during the 17 year-interval of 1981–1997. The distribution of the cases in different age groups is shown in Table 1.

**Table 1** Age and gender distribution of all cases between 1981–1997 in South Hungary

| Age (year) | Girls | Boys | All Children |
|---|---|---|---|
| <1 | 3 | 3 | 6 |
| 1 | 9 | 12 | 21 |
| 2 | 18 | 15 | 33 |
| 3 | 14 | 17 | 31 |
| 4 | 14 | 16 | 30 |
| Total | 58 | 63 | 121 |

The monthly number of cases and births in the period 1981–1997 are displayed in Table 2. Firstly, we tested whether there is a seasonal pattern with one maximum level and one minimum level per year. There was no evidence of seasonality of birth for ALL in all children ($P$=0.37). However, in the gender specific analyses, a cyclical pattern of a simple harmonic curve was found for girls ($P$=0.023) with a maximum incidence rate in November and a minimum incidence rate in May (Fig. 1). The amplitude α was 0.57, implying a 57% difference in rates from the mean to the maximum.

The use of different time sectors: 2 months and 2 weeks, had no influence of the seasonal pattern observed.

The logistic regression model was used to test further for seasonality using sine and cosine functions with 6 month period. There was a cyclic pattern for ALL in all children diagnosed under age 5 years (Fig. 2). There were two peaks in early February and early August, and two troughs in May and November with an amplitude of 0.32 ($P$=0.034).

In the gender specific analyses, a similar cyclic pattern ($P$= 0.09) was found for boys (two peaks in early February and early August, and two troughs in May and November), but no cyclic pattern was for girls (Fig. 3.). All models had a good fit.

No evidence was found for seasonality of the date of diagnosis.

## Discussion

### Main Findings

The pattern of annual cyclical variation in incidence of childhood ALL was studied both in birth month and month of first diagnosis during the period 1981–1997. We found no seasonal effect related to date of diagnosis. However, there was seasonal variability for ALL related to date of birth of all children diagnosed under age 5 years. Maximal rates were in children born in February and August in the simple harmonic regression model for all cases. A similar seasonality pattern of a borderline significance was found for boys in a gender specific analysis. However, for girls a different seasonality

**Table 2** Number of births and cases of *all*, among boys and girls born between 1981–1997 and diagnosed before the end of 2002

| | No. of *all* cases | | | No. of births | | |
|---|---|---|---|---|---|---|
| Month | Boys | Girls | Total cases | Boys | Girls | All children |
| 1 | 6 | 8 | 14 | 21,093 | 20,027 | 41,120 |
| 2 | 8 | 6 | 14 | 19,489 | 18,490 | 37,979 |
| 3 | 6 | 5 | 11 | 21,211 | 20,134 | 41,345 |
| 4 | 5 | 2 | 7 | 19,637 | 18,635 | 38,272 |
| 5 | 2 | 1 | 3 | 20,486 | 19,428 | 39,914 |
| 6 | 7 | 1 | 8 | 20,488 | 19,435 | 39,923 |
| 7 | 8 | 6 | 14 | 22,376 | 21,243 | 43,619 |
| 8 | 5 | 7 | 12 | 21,580 | 20,481 | 42,061 |
| 9 | 5 | 5 | 10 | 21,256 | 20,177 | 41,433 |
| 10 | 3 | 8 | 11 | 20,214 | 19,180 | 39,394 |
| 11 | 5 | 6 | 11 | 19,429 | 18,434 | 37,863 |
| 12 | 3 | 3 | 6 | 20,039 | 19,022 | 39,061 |
| Total | 63 | 58 | 121 | 247,298 | 234,686 | 481,984 |

pattern was found with a maximum level in November and a minimum level in May. These findings were consistent when different temporal units were used.

## Strengths and Weaknesses

The establishment of the national oncologic care system in the early 1970s, regional registration and regular updating of patients' files provides a high level of completeness of ascertainment of leukaemia cases over a long time period in Hungary [7]. This regional registration 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 the childhood population over a 17 year period of time.

In our study the population denominator was accurately known but in the gender specific analyses we used the exact annual male: female ratio to estimate the number of births for each subgroup.

Using a 6 month period described by sine and cosine functions statistically significant monthly variation in the date of birth of children aged under 5 years diagnosed with ALL was seen. Our study was the first to investigate gender specific cyclical patterns.

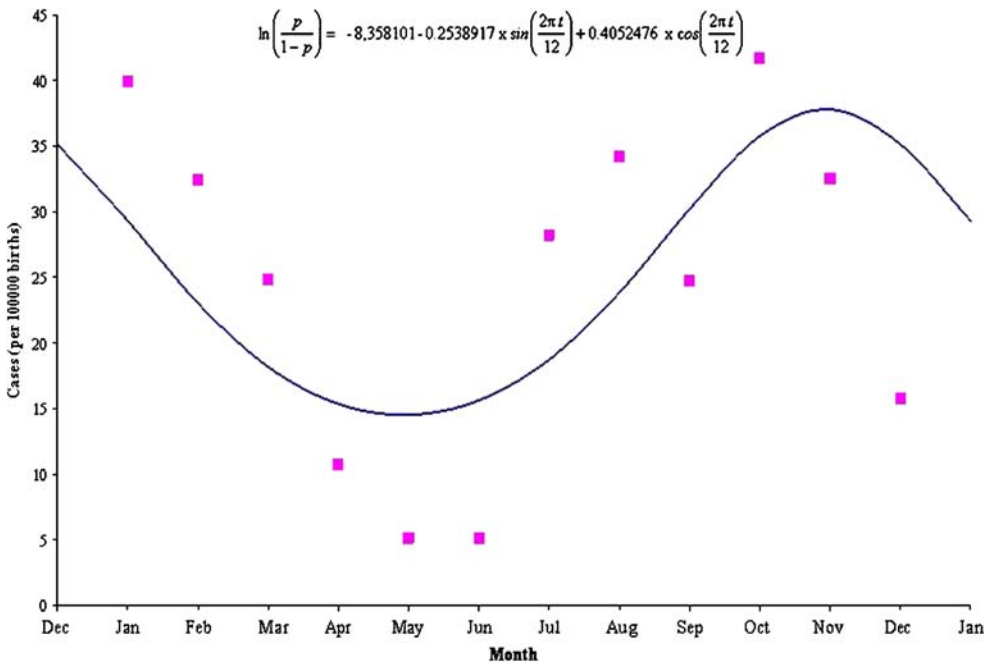


**Fig. 1** Seasonal variation in month of birth in girls aged under 5 years diagnosed with ALL

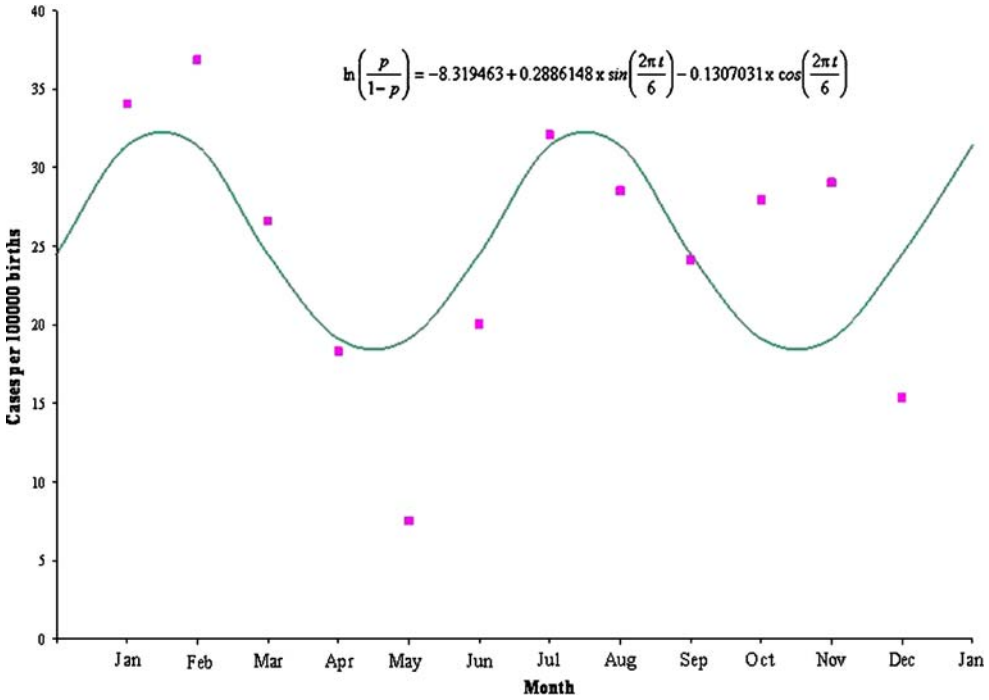


**Fig. 2** Seasonal variation in month of birth in children aged under 5 years diagnosed with ALL

## Comparison with Other Studies

An investigation of seasonality stands as an important component in the understanding of the aetiology description of certain childhood cancers. If early exposure to infections is involved in the aetiology of childhood leukaemia then seasonal variation in the time of birth could be expected, but only if the causal exposure is one for which there is seasonal variation in prevalence. Previous studies that have examined seasonality of time of birth in relation to childhood ALL have produced conflicting results. A study of seasonal variation related to date of diagnosis from Hungary showed no effect [10]. The authors analyzed 814 children, 0–18 years of age, in whom ALL was diagnosed in the period between the 1st of January 1988 and 31st of December 2000. In our study we found

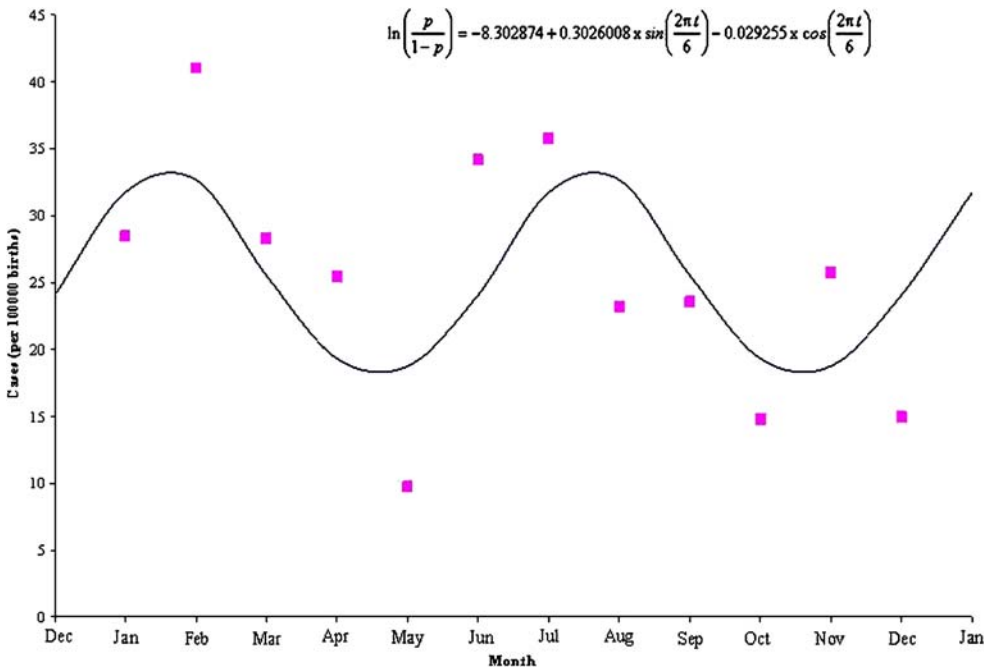


**Fig. 3** Seasonal variation in month of birth in boys aged under 5 years diagnosed with ALL

also no seasonal effect related to date of diagnosis although we used a longer time period and only included cases aged under 5 years. In contrast evidence of seasonality in the date of first symptom or of diagnosis have been found in several previous studies. In a study from North West England, Westerbeek et al. [11] found a cyclic effect related to ALL with a peak in November. Badrinath et al. [12] analysed the month of diagnosis of acute leukaemia in East Anglia, UK, for the period 1971–1994, and showed a significant summer excess for ALL in children. A summer peak was also found in a study from the USA [13]. ALL also demonstrated statistically significant monthly variation in the date of appearance of the first symptom (peak in October) and the date of diagnosis (peak in November) in an Iranian study [14].

There was evidence of seasonality in date of birth in studies from Denmark [15] and the UK, although there was variability in the time of peak incidence [16, 17]. The Danish study of children aged under 4 years diagnosed with ALL found marked seasonality in birth with a peak in April. A February peak was found in Northern England, UK, in a study of children diagnosed with ALL aged 1–6 years [16], and in a study of 15,835 cases of childhood leukaemia born and diagnosed in the UK between 1953–1995 [17].

We found evidence of seasonality related to month of birth with peaks in February and August. Both peaks correspond to previous findings and could reflect the seasonality of infectious diseases in temperate climates: respiratory virus infections (for example, influenza, parainfluenza, respiratory syncytial virus) show marked seasonality occurring in the winter months, and gastrointestinal infections peaks in the summer months [18].

In the gender specific analyses different types of seasonal evidence were seen for boys and girls. Two peaks in early February and early August, and two nadirs in May and November were in the simple harmonic regression model for boys and a cyclic pattern of a simple harmonic curve was found for girls with a maximum incidence rate in November. These findings could confirm the impression that males are more susceptible than females to some infectious diseases [19–22]. Gender differences in disease incidence may provide important clues to the pathogenesis of diseases and further research on this subject should be encouraged.

Seasonal variation related to time of birth would indicate exposure to an infection *in utero* or around the time of birth. There are two hypotheses about the role of infection in the etiology of leukemia. Kinlen [23] proposed that childhood leukemia could be a rare response to *in utero* or postnatal infectious exposure. In contrast, Greaves [24] postulated that an initial mutational event occurs *in utero* then subsequent mutations occur after birth which are strongly influenced by the timing of exposure to infectious agents in infancy. Our study provides some evidence of different types of exposure to infections around the time of birth in the gender specific analyses which in part, could explain the male predominance in the incidence of ALL.

## Conclusions

There was evidence of seasonality of birth in children, aged under 5 years, who developed ALL. Our findings confirm the suggestion that males are more susceptible than females to a putative infectious exposure. However, the gender-specific pathogenesis of ALL requires further investigation.

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