Space–time clustering of childhood lymphatic leukaemias and non-Hodgkin’s lymphomas in Sweden

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Abstract. Background: The discussion concerning clusters of childhood leukaemia has mainly been focused on their relation to the time and place of diagnosis. Recently some studies have indicated clustering not only at diagnosis, but also around time and place of birth. Space–time clustering at time of birth could be of special interest if the aetiological agent is of infectious origin and the induction of leukaemia either occurs pre- or perinatally or an infection at that time favours a poor subsequent immune response to the agent. Methods: To identify possible space–time clustering we have used the close-pair method of Knox. One-thousand-twenty recorded cases (0–14 years) of childhood acute lymphatic leukaemia and 293 cases (0–14 years) of malignant non-Hodgkin’s lymphoma from Sweden between 1973–1996 were analysed. The records include date of birth and of diagnosis as well as addresses at birth and at diagnosis. Results: A significant excess of case-pairs (25 observed, 14.9 expected, p = 0.01) was observed close in date and place of birth in the 4–14 year age group with acute lymphatic leukaemia (ALL). However there was no statistically significant clustering found around time of diagnosis. When the cases of leukaemia and the non-Hodgkin’s lymphomas were combined no statistically significant clustering was obtained neither at birth nor at diagnosis. Conclusions: This study strengthens the evidence of space–time clustering around the birth date in children whom later developed ALL. This observation is in support of the hypothesis that pre- or perinatal infections can induce a process leading to ALL.

Key words: Childhood ALL, Non-Hodgkin’s lymphomas, Space–time clustering, Viral hypothesis

Introduction

Certain inherited congenital conditions, exposure to ionising radiation and chemotherapeutic agents are known causes of childhood leukaemia. These factors, however, can only explain a minority of cases and the aetiology of the majority of cases remains unexplained [1]. The suggestion that an infectious agent may play a part in the aetiology of leukaemia is suggested because of the epidemiological characteristics of this disease.

Recent studies have shown that some paediatric acute lymphatic leukaemias (ALLs) are initiated prenatally at a very early stage of foetal haematopoesis [2, 3]. However, probably a secondary postnatal molecular event is required for the preleukemic clone to expand. The second event, leading to leukaemia, occurs at a time of maximum stress on lymphocytic precursor proliferation and may be promoted by exposure to a common infectious agent [2, 4].

Early suspicions of the existence of an infectious agent in childhood leukaemia have to a great extent relied on reports of clusters, usually a high number of cases occurring in a small area over a limited period of time. The validity of these findings has been questioned by several authors [5, 6]. But recent results of a series of large space–time studies in Britain [7–9] and Greece [10, 11] have strengthened the evidence for the existence of space–time clustering. One space–time analysis using a modified Knox method has also recently been replicated in the ‘EUROCLUS’ project [12]. This project included 13,351 cases of childhood leukaemia diagnosed during 1980–1989 in defined geographical regions in 17 countries. The results indicate statistically significant evidence of clustering of ALL in infants and older children around the time of birth and of the childhood peak cases around the time of diagnosis. Variations in incidence were also positively correlated with population density [13].

Although most reports have emphasised space–time clustering at diagnosis, other recent British studies have found space–time clustering at the time around birth [14–16]. A newly published study from New Zealand, also indicates significant space clustering at birth in a subgroup of leukaemias 10–14 years of age [17].

In a previous study we have studied 645 recorded cases of childhood acute lymphatic leukaemia in Sweden 1973–1989, in order to identify space–time clustering by using the close-pair method of Knox.
There was a significant excess of case-pairs close in date and place of birth in the 5–15 age group [18]. The present study was extended to include both lymphatic leukaemias as well as non-Hodgkin’s lymphomas during a wider time span, 1973–1996, applying the same statistical method.

The non-Hodgkin’s lymphomas were included since this malignant proliferation shares the cellular origin with lymphatic leukaemias and many of the immunohistochemical and biological markers [19].

Materials and methods

The patient material comprised 1020 children with ALL, 237 children with acute unspecified leukaemia and 293 children with non-Hodgkin’s lymphoma. The patients were born between 1973 and 1996 in Sweden and were 0–14 years of age.

Information on age and addresses at diagnosis of the cases were obtained from the Swedish Cancer Registry, which is a compulsory register of cancers including practically all cases of malignancies during this period [20]. The birth addresses were obtained from the Swedish Medical Birth Registry, which is a standardised set of medical records introduced in Sweden in 1973 [21]. The age groups, for identifying space–time clustering included the following strata: 0–14, 0–4 years and analyses for the childhood peak were defined in three ways (1–5, 2–4, 2–6 years). In conformity with the EUROCLUS protocol the infant group was defined as 0–1 years [12] and the older age were defined according to Alexander [13], 5–14 years, but we expanded the group to also include ages 4–14 years.

Knox’s method for detecting space–time clustering was used for the statistical analysis [22]. With the Knox approach, two cases are considered to be close if they reside in both a specified spatial and a temporal distance of each other. All possible pairs of cases are assembled and classified according to their distances apart in time and space. The possible pairs considered are \( n(n−1)/2 \) pairs for \( n \) observed cases of leukaemia. The observed number of pairs is compared with the expected number. Numbers of observed pairs are not additive if we divide the big group into smaller age groups. The significance of the observed number of close pairs compared with the expected number of pairs is tested.

Five critical intervals between dates of diagnosis (or birth) were used: 1, 3, 6, 12 and 24 months. Pairs of cases diagnosed (or born) within the same municipality were considered as close in space. We used the definition of municipalities from 1977, which divides Sweden into 277 municipalities. The mean number of inhabitants was 30,000 (range 4000–700,000) and the mean area was 1486 km² (range 9–19, 447 km²). The statistical significance was determined assuming Poisson variation.

Results

The results of the analysis indicate a significant clustering of pairs residing within the same municipality and born within 1 month of each other within the 4–14 years age group with ALL (25 observed close pairs against an expected value of 15; \( p = 0.01 \), Table 1). Even after accounting for multiple testing using Bonferroni’s rule (by multiplying this \( p \) value with the number of critical time intervals tested) there was still a clear significance for clustering (adjusted \( p = 5 \times 0.01 = 0.05 \)).

In contrast, neither among children 0–14, 0–4, 0–1, 1–5, 2–4 nor 2–6 years there was any significant space–time clustering at birth.

If we included the acute unspecified leukaemias we found less significant results (observed number of case-pairs = 26, expected number = 16.5, \( p = 0.04 \) in the 4–14 years age group).

When we included the non-Hodgkin’s lymphoma we could not find any clustering in the combined group (Table 2).

Linkage according to municipality at diagnosis and date of diagnosis among children in the corresponding groups showed no significant excess of case-pairs.

Discussion

The evidence of an infectious aetiology for childhood acute lymphoblastic leukaemia has grown in the past decade. A possible variability of the latent period makes it difficult to detect clustering of the etiological factor of the disease, using date and place of diagnosis, because cases that were initiated together would not necessarily manifest their disease at the same time. A search for clustering by date and place of birth invokes the theory that most cases of childhood ALL (cALL) are determined pre- or perinatally when the human organism is particularly susceptible to endogenous and exogenous genotoxic effects [23]. Gutrie cards from new-borns that subsequently developed cALL with TEL-AML fusion gene showed that eight out of eleven patients, including a pair of twins, had the same clonotypic TEL-AML genomic sequence at birth. Three other patients diagnosed with MLL-AF4 fusion gene ALL also gave positive PCR signals from blood spots at birth [3]. These studies confirm that some paediatric ALL are initiated at a very early stage of foetal haematopoiesis. However the causal events that give rise to preleukaemic cells are unknown. The biological and clinical variety of leukaemia in infants, during childhood peak and in older children is such that it would be remarkable if they all share one causal mechanism. A candidate infectious agent could be transmitted from the mother to the foetus, affecting a sensitive stage of foetal B-cell differentiation, but such a virus could also be involved in a postnatal event. Tentatively the