

Time space distribution of childhood leukaemia in the Netherlands

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SUMMARY In the western part of the Netherlands during 1973–80 leukaemia was diagnosed in 293 patients aged under 15 years. An overall incidence rate of 2.91 per 100 000 person years was calculated. No seasonal influence on months of birth or months of diagnosis of these patients could be traced by the method of Edwards. Time space clustering was looked for by both methods of Mantel and Knox. No significant time space clustering of date and place of diagnosis of childhood leukaemia was found in all types of leukaemia, acute lymphocytic leukaemia (ALL), ALL in boys and girls, ALL in children under 6 years at diagnosis, and in acute non-lymphocytic leukaemia.

The results of studies of temporal and spatial distribution of childhood leukaemia are not consistent and are even contradictory.¹ Clustering of cases might be caused by an environmental agent acting in a limited geographical area for a limited period. This could be most easily detected in childhood leukaemia because of the limited mobility of children compared with adults, which may facilitate the observation of clusters.

The existence of a complete seven year nation wide registry of childhood leukaemia offered us the opportunity to look for time space clustering in the densely populated western part of the country.

Material and methods

The morbidity registry of the Dutch Childhood Leukaemia Study Group (DCLSG) was established in 1972. It covers the whole country, which in 1976 had a childhood population (< 15 years) of nearly 3.4m (total population 13.9m).

Nearly 160 paediatricians in the Netherlands collaborate in the DCLSG in an effort to optimise the treatment of children with leukaemia. They routinely send blood and bone marrow slides of each child with leukaemia or under suspicion of this disease to the DCLSG laboratory. These slides are reviewed according to previously determined criteria by two independent experts. Before 1975 the DCLSG laboratory used its own diagnostic criteria based on morphology and cytochemistry (Sudan black and periodic acid-Schiff (PAS)). Since 1975 the

French-American-British (FAB) classification has been used.^{2,3} The treatment of these children is centrally coordinated and clinical information is uniformly collected.

In 1980 the completeness of the morbidity registration was checked by sending a questionnaire to all 462 paediatricians in the Netherlands. They were asked to give the names, dates of birth, dates of diagnosis, and sex of all patients with leukaemia whom they had treated or consulted between 1973 and 1980. The overall response rate to the questionnaire was 92.6%, and 17 cases, hitherto unknown, were reported. Bone marrow slides of 12 of these patients were still available, and the diagnosis of leukaemia could be confirmed at the DCLSG laboratory. We estimate that over 95% ascertainment of patients had been achieved in the period 1973–80.

The patients with leukaemia who were accepted for this study were all under 15 at the time of diagnosis (1 January 1973 until 1 January 1980). The diagnosis was confirmed by bone marrow slides at the DCLSG laboratory. The cluster analysis was limited to the western part of the Netherlands, comprising the provinces of North Holland, South Holland, and Utrecht, because the home address at diagnosis of each patient could be located on a geographical map with a scale of 1:50 000. Within this map the addresses in larger towns were identified with the use of large scale street maps. This part of the Netherlands covers about 7677 sq km. In 1976 the childhood population (0–15 years) was 1.44m. It has

the highest population density in the Netherlands and is nearly uniformly urbanised. This has the advantage that the same distance between patients does have an equal meaning.

For the cluster analysis, the date of the diagnostic bone marrow sample was chosen, and this represents the date of diagnosis. A seasonal trend in month of birth or month of diagnosis of leukaemic patients was examined by using the analysis of monthly frequencies of Edwards.⁴

The methods of Knox⁵ and Mantel⁶ were used to investigate time space interaction. Both analyses are based on examination of time and distance intervals between all possible pairs of cases. The hypothesis that pairs of patients who are close in time are also close in space is tested. Mantel's method uses a time versus space regression. For each possible pair of patients, say patient *i* and patient *j*, a spatial measure of X_{ij} and a temporal measure Y_{ij} is obtained. A clustering measure is given by test statistic:

$$Z = X_{ij} \cdot Y_{ij}$$

Evidence of time space clustering is given if the observed Z differs significantly from the permutational expectation of Z

$$\chi = \frac{Z - E(Z)}{SE(Z)}$$

In concept, the set of time and space locations for the patients are split apart and then put back together at random. Each possible way of putting them back together results in a new value for Z . Mantel⁶ describes how to determine approximately the expected Z and the standard error of Z under normal assumptions, so that the departure of the observed Z from its expected value can be tested for significance.

In this study the reciprocal value of time and distance intervals between pairs of patients was used in Mantel's cluster analysis. In this way the short distances will be spread out while collapsing the range of great distances. Temporal and space distances equal to zero were replaced by the value 3.

In the method of Knox⁵ each pair is classified as being close or far apart in time and close or far apart in space to form a 2x2 contingency table. The expected number of pairs may be calculated from the marginal totals. The observed number of close pairs is tested as a Poisson deviate from the expected number. In this model critical time and distance intervals are arbitrarily chosen.

In our analysis 2 km distance intervals (2, 4, 6, 8,

and 10) and time intervals of two months (2, 4, 6, 8, 10, and 12) were used.

Analyses according to Edwards,⁴ Knox⁵ and Mantel⁶ were performed for the total group of patients and for different subgroups classified according to type of leukaemia, tumour load (initial leucocyte counts over 50 000/mm³), age (younger than 6 years at diagnosis⁶⁻⁸), and sex.

Results

During 1973-80 in the western part of the Netherlands leukaemia was diagnosed in 293 patients aged under 15 years. This amounts to an incidence rate of 2.91 per 100 000 person years (standard error (SE) = 0.17). Acute lymphocytic leukaemia (ALL) was the most common type compared with acute non-lymphocytic leukaemia (ANLL) and chronic myeloid leukaemia (CML, including the juvenile and adult type)—that is, 79.5%, 16.7%, and 2.4%, respectively. In 1.4% the type could not be classified.

The patients' months of diagnosis or months of birth were examined for evidence of a seasonal trend. The analyses were performed for all patients, patients with ALL, the subgroups of boys and girls with ALL, patients with ALL younger than 6 years at diagnosis, patients with initial counts $\geq 50\ 000$ leucocytes/mm³, and patients with ANLL. No significant seasonal variation was found. Table 1 gives the results for ALL.

Table 2 gives the results of time space clustering using Mantel's method. No significant clustering of date and place of diagnosis was detected—neither for all leukaemic patients nor for the different subgroups of patients (all *p* values for analysis > 0.10).

Table 3 shows the results of Knox's analysis of children with leukaemia at a critical space distance of 2 km and three critical time distances of two, four, and six months. The null expectation did not show a departure from the observed number of close pairs classified according to type, age, and sex (*p* values > 0.10). Only clustering of patients with ALL with initial count $\geq 50\ 000$ leucocytes/mm³ was found. This consists of a higher number of pairs with a distance separation of under 2 km and a time separation of under six months. Four pairs were found while the expected number was 1.4. This difference was statistically significant ($\chi = 2.20$, one-sided $p < 0.025$).

Discussion

Knox⁵ did not find a seasonal influence on the months

*Detailed tables with all performed time space cluster analyses according to Knox⁵ and Mantel⁶ are available on request.

Table 1 Seasonal incidence of acute lymphocytic leukaemia

	Months											
	1	2	3	4	5	6	7	8	9	10	11	12
With regard to diagnosis	17	23	22	16	19	18	20	20	15	17	29	17
With regard to birth	26	17	12	16	24	28	9	25	14	27	20	15

Table 2 Time space cluster analysis by Mantel's method*

	All types	ALL	ALL (boys)	ALL (girls)	ALL (<6 years)	ALL (≥50 000/mm ³)	ANLL
No	293	233	133	100	159	43	49
Z	20.91	12.17	3.51	2.50	5.37	0.71	0.50
E(Z)	21.90	13.64	3.94	2.93	6.17	0.52	0.55
SE	1.75	1.29	0.57	0.89	0.72	0.39	0.15
χ	- 0.56	- 1.14	-0.75	-0.48	1.11	0.49	0.33

ALL = Acute lymphocytic leukaemia.
ANLL = Acute non-lymphocytic leukaemia.

Table 3 Time space cluster analysis by Knox's method

Time separations between pairs of cases in months	≤2 km space separation between pairs of cases						
	All types	ALL	ALL (boys)	ALL (girls)	ALL (<6 years)	ALL (≥50 000/mm ³)	ANLL
≤2 Obs	12	6	0	1	2	1	0
Exp	13.5	9.00	2.3	2.2	3.6	0.4	0.2
χ	- 0.41	- 1.00	-1.52	-0.81	-0.84	0.95	-0.45
≤4 Obs	27	15	0	4	4	1	0
Exp	26.3	17.4	4.2	4.3	6.8	0.9	0.5
χ	0.14	- 0.58	-2.05	-0.14	-1.07	0.10	-0.71
≤6 Obs	40	26	3	5	6	4	0
Exp	39.2	25.8	6.3	6.2	9.9	1.4	0.7
χ	0.13	0.04	-1.31	-0.48	-1.24	2.20*	-0.84

*Significant p<0.025.
ALL = Acute lymphocytic leukaemia.
ANLL = Acute non-lymphocytic leukaemia.

of birth for children with leukaemia. This agrees with our result. Most previous investigations,⁷⁻¹⁰ except one study in England,⁵ did not establish any significant seasonal variation for the months of diagnosis. Neither in this study was any seasonal influence on the month of diagnosis found.

Knox⁵ in Northumberland and Durham, Till *et al*⁷ in London, and Gunz and Spears⁸ in New Zealand detected weak evidence of clustering of date and place of diagnosis in patients with leukaemia aged under 6 years at diagnosis with Knox's statistical method. In London even clustering of date and place of birth was shown. Mantel's cluster analysis was also used on the data in New Zealand.⁹ The results confirm time and space clustering of childhood leukaemia. The authors, however, suggest that this finding is perhaps due to shifting population patterns and unequal population growth.

In Connecticut¹⁰ and Michigan¹¹ cases of childhood leukaemia were analysed for time space interaction.

In these studies discrete units of space function as cells in which the distribution of the patients over time is tested for random distribution. The time and distance boundaries were arbitrarily chosen. The results show no significant clustering.

In San Francisco¹² and Lewisham¹³ no time space interaction of childhood leukaemia was detected with Knox's method.

A reanalysis of the death certificates of leukaemic children in London with a generalised approach of Knox's analysis in which time and distance intervals and arbitrary periods of latency and susceptibility of leukaemia were taken into account established no evidence of time space clustering.¹⁴

The studies about time space clustering in childhood leukaemia have either produced negative findings or weak positive findings. In this study we found no evidence for time space clustering in the total group of patients nor in the subgroups classified according to type, age, and sex.

The method of analysis can influence the results of time space clustering. In the western part of the Netherlands time space analysis of leukaemic patients do only show clustering with Knox's method for patients with ALL with high initial leucocyte counts ($\geq 50\ 000/\text{mm}^3$). Mantel's method, however, could not confirm this finding. Considering the exploratory nature of Knox's analysis, which uses varying critical distance intervals, the clustering could be a chance event.

In the Netherlands we found no seasonal variation in months of birth or months of diagnosis of children with leukaemia. Also no significant time space clustering of childhood leukaemia was traced. The restrictions of the statistical methods of cluster analysis have to be taken into account. Long latency periods of aetiological factors could mask clustering. Furthermore, the patients were classified according to cytomorphological criteria and one wonders if these subgroups with leukaemia are homogeneous with regard to the aetiology.

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