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Is there a common aetiology for certain childhood malignancies? Results of cross-space–time clustering analyses

Richard J.Q. McNally [a,*], Tim O.B. Eden [b], Freda E. Alexander [c], Anna M. Kelsey [d], Jillian M. Birch [e]

[a] *Sir James Spence Institute, Level 4, Royal Victoria Infirmary, Queen Victoria Road, Newcastle NE1 4LP, UK*
[b] *Academic Unit of Paediatric Oncology, Central Manchester and Manchester Children's University Hospitals NHS Trust and Christie Hospital Trust, Wilmslow Road, Manchester M20 4BX, UK*
[c] *Department of Public Health Sciences, The University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG, UK*
[d] *Department of Histopathology, Central Manchester and Manchester Children's University Hospitals NHS Trust, Manchester M27 4HA, UK*
[e] *Cancer Research UK Paediatric and Familial Cancer Research Group, Central Manchester and Manchester Children's University Hospitals NHS Trust, Manchester M27 4HA, UK*

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Abstract

We previously demonstrated significant space–time clustering amongst cases of childhood leukaemia (in particular acute lymphoblastic leukaemia (ALL)), central nervous system (CNS) tumour (especially astrocytoma), soft tissue sarcoma and Wilms' tumour. We hypothesised that there may be common aetiological mechanisms between some of these diagnostic groups. To test this hypothesis we analysed for cross-space–time clustering between these diagnostic groups, using population-based data from north-west England. Data were examined by a second-order procedure based on K-functions. Reference points in time and space were dates and addresses at birth and diagnosis. The results showed statistically significant ($P < 0.05$) cross-clustering between cases of leukaemia and CNS tumour and between cases of ALL and astrocytoma. There was no statistically significant cross-clustering of Wilms' tumours and soft tissue sarcomas with any other malignancy. In conclusion, these findings are consistent with common, possibly infectious, aetiological mechanisms for childhood leukaemia (particularly ALL) and CNS tumours (particularly astrocytoma).

Keywords: Aetiology; Children; Environment; Epidemiology; Infection; Space–time clustering

1. Introduction

The aetiology of most childhood tumours remains unclear. Genetic predisposition is reported to be directly associated with about 5% of cases [1], whilst environmental exposure or host response to such exposure (genetically determined) is proposed for the majority. The onset of many childhood cancers during the first 5 years of life is suggestive of a pre-natal origin. It is clearly possible that both pre-natal and post-natal environmental exposures may play a key role in triggering the onset of different tumour types. It is thought that the process leading to the onset of childhood cancer will involve at least two events [2,3]. The postulate is that whilst the first event may be inherited or somatic due to endogenous or environmental factors, the final 'critical' event may involve an environmental factor. Both events would lead to cellular genetic changes and/or proliferation of pre-malignant clones.

If environmental factors are involved in the aetiology of childhood cancers, the cases might be expected to exhibit a non-random geographical distribution. Space–

* Corresponding author. Tel.: +44 191 202 3029; fax: +44 191 202 3060.
E-mail address: Richard.McNally@ncl.ac.uk (R.J.Q. McNally).

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time clustering is said to occur when there is an irregular distribution of cases simultaneously both in time and space. Such an irregular distribution may arise from a small number of large excesses or a large number of small excesses. This type of clustering would be expected to occur amongst particular diagnostic types that share a common environmental aetiology and is characteristic of infectious diseases.

We have previously found space–time clustering amongst cases of leukaemia, particularly acute lymphoblastic leukaemia (ALL), central nervous system (CNS) tumours overall and specifically astrocytoma, Wilms' tumour and soft tissue sarcoma in north-west England [4–7]. We have also reported seasonal variation in ALL and CNS tumours [5,8]. Furthermore, we have found an increased incidence of Wilms' tumour and soft tissue sarcoma in more affluent areas [9]. Taken together these findings suggest that environmental factors are involved in the aetiology of these tumours. Indeed a role for infections has been proposed for childhood leukaemia [10]. Furthermore, there has been speculation that certain viruses may be involved in the aetiology of CNS tumours [11].

We have now examined incidence data from the Manchester Children's Tumour Registry (MCTR) for the presence of cross-space–time clustering (hereafter for brevity simply termed cross-clustering) between cases from different diagnostic groups or sub-groups, using recently developed and rigorous statistical methods. The MCTR is population-based and contains high-quality verified diagnostic data.

Ascertainment of cases has been consistently high throughout the existence of the MCTR, even during the early years [12]. The aims of our study were to test predictions of cross-clustering that might arise as a result of common environmental exposures, such as infections. In addition, we aimed to formulate aetiological hypotheses for testing in further studies. If infections are involved in aetiology, then support for a pre-natal exposure would suggest a role for a directly transforming virus, whilst evidence of a post-natal exposure would support either a role for a directly transforming virus or for an indirect mechanism mediated by immune responses, as has been postulated for childhood peak ALL [3,13].

Based on our previous findings of space–time clustering and seasonality from the MCTR [4–8] and other studies that suggest an infectious aetiology [10,11,14] we predicted that there might be common infectious aetiological mechanisms for certain leukaemias (especially ALL), CNS tumours (especially astrocytoma), soft tissue sarcomas and Wilms' tumour.

2. Patients and methods

All cases of leukaemia, CNS tumour, Wilms' tumour and soft tissue sarcoma in 0–14-year-olds, diagnosed between 1st January 1954 and 31st December 1998, registered by the MCTR were analysed. Reporting practice to the registry has been consistently good throughout this period. The registry retains haematological and histopathological material and diagnostic re-review is undertaken periodically. For each case, Ordnance Survey (OS) four-digit Easting and four-digit Northing grid references were allocated to the centroid of the postcode of the addresses at time of birth and diagnosis. This allowed spatial referencing of the Easting and Northing co-ordinates to within 0.1 km. The analyses were restricted to those diagnostic groups (and sub-groups) that had exhibited within group space–time clustering [4–7]. The primary analyses considered cross-clustering between the main diagnostic groups: (i) leukaemias; (ii) central nervous system tumours (CNS); (iii) Wilms' tumours (WT); (iv) soft tissue sarcomas (STS).

There are four possible space–time interactions between: (i) times and places of birth; (ii) time of diagnosis and place of birth; (iii) times and places of diagnosis; (iv) time of birth and place of diagnosis. The interpretation of these interactions will depend on the extent of migration between birth and diagnosis among cases [4]. Interaction (i) addresses the hypothesis of a common pre-natal exposure, whilst both (ii) and (iii) address the hypothesis of a common post-natal exposure. Furthermore, (ii) is consistent with a common exposure around the place of birth, with a constant lag time between exposure and onset of a cancer. Interaction (iv) is not consistent with any plausible hypothesis and is not considered further.

Cross-clustering analyses were performed to test for associations between cases from different diagnostic groups. In this situation the test is concerned with clustering pairs 'a, b', where 'a' represents a case of disease 'a' and 'b' represents a case of a different disease 'b'. This differs from the previously published analyses [4–7], which were concerned with clustering pairs 'a, a' and 'b, b'. The analyses presented are based on K-functions [15]. K-function analysis is a generalisation of the Knox test [16]. The procedure used in the present analyses uses a set of 225 Knox-type calculations, where the thresholds change over a pre-specified set of values (for close times, $t = 0.1, 0.2 \ldots 1.5$ years and for close in space, $s =$ distance to the nth, $(n{+}1)$th$\ldots(n+14)$th nearest neighbour, where n was chosen as explained below). P-values were obtained by simulation. Any specified distance between two cases will have different interpretations in sparsely and densely populated areas. Furthermore, clustering may be affected by variability in the density of the study population. The distribution of case addresses was used as a proxy for population distribution. To adjust for different levels of population density, the geographical distance thresholds were chosen to be the maximum of the distances to the nth (and $(n+1)$th$\ldots(n+14)$th) nearest neighbour (NN) of

each of the pair, using all locations of all the cases of childhood cancer in the MCTR population-based data set, 1954–1998, except addresses for the same child at a different time. n (and $(n+1)\ldots(n+14)$) took the values 112, 113,...,126 for birth locations and the values 114, 115,...,128 for diagnosis locations. On average, the distance to the 119th nearest neighbour for birth locations and the 121st nearest neighbour for diagnosis locations was 5 km. This approach, known as the NN threshold method, was similar to the method proposed by Jacquez [17]. The K-function analysis gives no indication of the size of the clustering effect. The P-values depend both on the effect size and on the statistical power, which depends on the number of cases. For statistically significant results only, a measure of the effect size was obtained. The magnitude of the excess was estimated by $S = [(O - E)/E] \times 100$. O and E were found from the Knox test. Boundaries were chosen as distance to the nth nearest neighbour (where $n = 119$ for birth locations and 121 for diagnosis locations) for 'close in space' and 1 year for 'close in time'. It is possible that S may be small when the effect size is large if the clustering occurs within other boundaries.

Only those pairs of diagnostic groups that exhibited cross-clustering with a significance level of $P < 0.05$ using the NN version of the K-function method were considered further. For such groups, additional analyses were carried out to test for cross-clustering between diagnostic sub-groups that had previously exhibited within group clustering.

3. Results

Our study included 1475 cases of leukaemia (of which 1177 were ALL), 1045 with CNS tumours (of which 422 were astrocytoma), 236 Wilms' tumours and 244 with soft tissue sarcomas.

Using time and place of birth (Tables 1 and 2), there was statistically significant cross-clustering between cases of leukaemia and CNS tumour ($P = 0.009$; $S = 8.1\%$) and between cases of ALL and astrocytoma ($P = 0.007$; $S = 13.4\%$). There was no evidence of cross-clustering for Wilms' tumours and soft tissue sarcomas based on time and place of birth.

Using time of diagnosis and place of birth (Tables 1 and 2), there was statistically significant cross-clustering between cases of leukaemia and CNS tumours ($P < 0.001$; $S = 7.5\%$) and between cases of ALL and astrocytoma ($P = 0.01$; $S = 6.6\%$). There was no evidence of cross-clustering for Wilms' tumours and soft tissue sarcomas based on time of diagnosis and place of birth.

Table 2
Further sub-analyses of cross-clustering between ALL and astrocytoma (P-values)

Groups	P-values[a,b]
Time and place of birth	
ALL × astrocytoma	$P = 0.007$[c]
ALL × pilocytic astrocytoma	$P = 0.06$
ALL × diffuse and high-grade astrocytoma	$P = 0.007$[c]
Time of diagnosis and place of birth	
ALL × astrocytoma	$P = 0.01$[c]
ALL × pilocytic astrocytoma	$P = 0.01$[c]
ALL × diffuse and high-grade astrocytoma	$P = 0.26$

ALL, acute lymphoblastic leukaemia.

[a] Cases are close in time if dates differ by $<t$, where t is in the range 1.1–1.5 years. $I = \int R(s,t)\,ds\,dt$, where $R(s,t) = [K(s,t) - K1(s)K2(t)]/\sqrt{[K1(s)K2(t)]}$. $K(s,t)$ = proportion of pairs whose distance apart is $\leqslant t$ in time and $\leqslant s$ in space. $K1(s)$ = proportion of pairs whose distance apart is $\leqslant s$, and $K2(t)$ = proportion of pairs whose distance apart is $\leqslant t$. P-value obtained by simulation (999 runs) with dates randomly re-allocated to the cases in the analysis.

[b] Cases are close in space if either is within the distance to the nth nearest neighbour of the other (in the total data set), where n is in the range 112–126 for birth and 114–128 for diagnosis.

[c] P-value <0.05.

Table 1
Results for main groups by different time and place references

Groups	Time and place of birth[a,b]	Time of diagnosis and place of birth[a,b]	Time and place of diagnosis[a,b]
Leukaemias × CNS	$P = 0.009$[c]	$P < 0.001$[c]	$P = 0.02$[c]
Leukaemias × WT	$P = 0.10$	$P = 0.51$	$P = 0.65$
Leukaemias × STS	$P = 0.45$	$P = 0.33$	$P = 0.32$
CNS × WT	$P = 0.98$	$P = 0.97$	$P = 0.84$
CNS × STS	$P = 0.28$	$P = 0.92$	$P = 0.86$
WT × STS	$P = 0.38$	$P = 0.28$	$P = 0.53$

P-values from K-function analysis with NN threshold.

NN, nearest neighbour; CNS, central nervous system; WT, Wilms' tumour; STS, soft tissue sarcomas.

[a] Cases are close in time if dates differ by $<t$, where t is in the range 1.1–1.5 years. $I = \int R(s,t)\,ds\,dt$, where $R(s,t) = [K(s,t) - K1(s)K2(t)]/\sqrt{[K1(s)K2(t)]}$. $K(s,t)$ = proportion of pairs whose distance apart is $\leqslant t$ in time and $\leqslant s$ in space. $K1(s)$ = proportion of pairs whose distance apart is $\leqslant s$, and $K2(t)$ = proportion of pairs whose distance apart is $\leqslant t$. P-value obtained by simulation (999 runs) with dates randomly re-allocated to the cases in the analysis.

[b] Cases are close in space if either is within the distance to the nth nearest neighbour of the other (in the total data set) where n is in the range 112–126 for birth and 114–128 for diagnosis.

[c] P-value < 0.05.

Table 3
Comparison of key results (*P*-values) by different time and place references

Groups	Time and place of birth[a,b]	Time of diagnosis and place of birth[a,b]	Time and place of diagnosis[a,b]
Leukaemias × CNS	$P < 0.001$[c]	$P = 0.009$[c]	$P = 0.02$[c]
ALL × astrocytoma	$P = 0.007$[c]	$P = 0.01$[c]	$P = 0.35$

ALL, acute lymphoblastic leukaemia; CNS, central nervous system.

[a] Cases are close in time if dates differ by $<t$, where t is in the range 1.1–1.5 years. $I = \int R(s,t)\,\mathrm{d}s\,\mathrm{d}t$, where $R(s,t) = [K(s,t) - K1(s)K2(t)]/\sqrt{[K1(s)K2(t)]}$. $K(s,t)$ = proportion of pairs whose distance apart is $\leqslant t$ in time and $\leqslant s$ in space. $K1(s)$ = proportion of pairs whose distance apart is $\leqslant s$, and $K2(t)$ = proportion of pairs whose distance apart is $\leqslant t$. *P*-value obtained by simulation (999 runs) with dates randomly re-allocated to the cases in the analysis.

[b] Cases are close in space if either is within the distance to the nth nearest neighbour of the other (in the total data set) where n is in the range 112–126 for birth and 114–128 for diagnosis.

[c] *P*-value < 0.05.

Using time and place of diagnosis (Table 1), there was statistically significant cross-clustering between cases of leukaemia and CNS tumour ($P = 0.02$; $S = 2.4\%$), but not between cases of ALL and astrocytoma. There was no evidence of cross-clustering for Wilms' tumours and soft tissue sarcomas based on time and place of diagnosis.

Further sub-analyses were performed to determine whether the cross-clustering between ALL and astrocytoma could be attributed to cross-clustering between ALL and pilocytic astrocytoma or between ALL and diffuse and high-grade astrocytoma (Table 2). Cross-clustering between ALL and astrocytoma only involved pilocytic astrocytoma at time of diagnosis and was more marked for diffuse and high-grade astrocytoma at time of birth. A comparison of key results (*P*-values) by different time and place references is given in Table 3.

4. Discussion

Previous studies from the MCTR have identified space–time clustering amongst cases of leukaemia, CNS tumours, soft tissue sarcomas and Wilms' tumours [4–7]. However, no previous study has systematically examined cross-clustering between cases from different diagnostic groups. For cross-clustering the test is concerned with clustering pairs 'a, b', where 'a' represents a case of disease 'a' and 'b' represents a case of a different disease 'b'. Thus, the analyses and results are entirely novel and do not duplicate any results from previous publications. Statistically significant results were restricted to cross-clustering involving cases of leukaemia and CNS tumour and there was no evidence for cross-clustering involving cases of WT and STS.

Previous studies from the MCTR have specifically shown space–time clustering and seasonality for ALL and astrocytoma [4–6,8]. In those studies clustering of ALL and astrocytoma was found both at time of birth and at time of diagnosis [4–6]. Furthermore, both pilocytic and diffuse and high-grade astrocytoma exhibited space–time clustering [5]. The present study found cross-clustering between ALL and astrocytoma (Table 2). Both pilocytic and diffuse and high-grade astrocytoma were shown to cross-cluster with ALL. Additionally, recent temporal increases in the incidence of ALL in the childhood peak [18] and in the incidence of astrocytoma have been identified [19]. Thus, there are a number of similarities in the incidence patterns of ALL and astrocytoma (both pilocytic and diffuse and high-grade).

Cross-clustering between leukaemia and CNS tumours was evident at all three time and place references (Table 3) but was most striking at those references that involved place of birth. Cross-clustering between ALL and astrocytoma only involved place of birth and not place of diagnosis. However, whilst cross-clustering between ALL and diffuse and high-grade astrocytoma was only found using time and place of birth, cross-clustering between ALL and pilocytic astrocytoma was more marked based on time of diagnosis and place of birth (Table 2). The strength of clustering result indicated that there was a 13.4% excess for cross-clustering pairs of ALL and astrocytoma. After allowing for the cases that were in more than one cross-clustering pair this excess involved approximately 10% of the astrocytoma cases and approximately 3% of the ALL cases.

There is strong evidence to suggest that infections may be involved in the aetiology of childhood leukaemias [10]. Indeed, three hypotheses have been proposed [3,20–22]. Kinlen [20,21] suggested that excesses of childhood leukaemia are associated with highly unusual population mixing; Greaves [3] proposed that higher incidence of precursor B-cell ALL is associated with delays in exposure to common infections; and Smith [22] suggested that childhood peak ALL is due to *in utero* exposure to infection. Furthermore, there is evidence from a number of studies linking non-specific infections to the aetiology of childhood brain tumours. Increased risk has been associated with neonatal infections, viral infections during pregnancy and exposure of the child to higher levels of community infections around birth [23–25]. Also, exposure of the mother during pregnancy and the child in the early years to farm animals (which may be taken as a proxy for exposure to infectious

agents) was associated with high risk of CNS tumours in the child [26,27]. By contrast, little or no associations with infection have been found for soft tissue sarcomas or Wilms' tumour [14].

Overall cross-clustering was mostly evident based on place of birth (especially between ALL and astrocytoma). This is consistent with an *in utero* or very early post-natal exposure to infection that leads to the onset of ALL [22]. It is also consistent with evidence linking infections during pregnancy or in the early years to increased risk of childhood brain tumours [23–27]. Taken together, all of this evidence suggests that an exposure to an infection during pregnancy or shortly after birth has a directly transforming effect and may lead either to ALL or astrocytoma. The evidence does not support a later exposure because there was no evidence for cross-clustering between ALL and astrocytoma based on time and place of diagnosis. Furthermore, a common exposure that affects different cell lineages pre-natally or shortly after birth is more biologically plausible than a common mechanism that affects different cell lineages at a later stage post-natally.

Our previous study of non-CNS solid tumours found space–time clustering amongst cases of WT and STS, by themselves [7]. Neither WT nor STS were involved in cross-clustering. Furthermore, the incidence rates for WT and STS have not displayed a temporal trend (no increase or decrease) but have been found to be higher in more affluent areas [9,19]. Thus, the incidence patterns differ, somewhat from the leukaemias and CNS tumours. We would hypothesise that, whilst there is evidence for environmental factors in aetiology, these are not shared with the leukaemias and CNS malignancies or with each other. Alternatively, it could indicate that different mechanisms are involved.

Future work should consider looking for common aetiological agents and mechanisms. One approach would be to analyse combined groups of tumours (such as ALL and astrocytoma) in case-control studies. Most case-control studies have analysed broad diagnostic groups separately (*e.g.*, leukaemia or CNS tumours). Some studies have used cases of cancer from diagnostic groups other than the one being studied as controls on the assumption that other diagnostic groups would have a different aetiology. The results from the present analyses would indicate that such an assumption may be erroneous. Furthermore, many case-control studies have not considered detailed diagnostic groups and subgroups as separate entities for analysis. This relied on assuming that the broader diagnostic groups did not have heterogeneous aetiologies. Again, the results from the present analyses show that this argument may be flawed.

The analyses presented here have been carried out on high-quality incidence data using rigorous statistical methodology. It should be noted that there could be some dilution of the population-base of birth addresses, due to migration out of the study region. However, such migration is likely to have a random and not a systematic pattern and is thus very unlikely to introduce artefactual cross-clustering.

In conclusion, these highly novel findings are consistent with a common infectious aetiology for childhood leukaemia and CNS tumours, and more especially for ALL and astrocytoma. We would speculate that around 10% of the astrocytoma cases and around 3% of the ALL cases may have arisen in this manner. Furthermore, there are implications for the design of future case-control studies, including the choice of control groups.

Conflict of interest statement

None declared.

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