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Further clues concerning the aetiology of childhood central nervous system tumours

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Abstract

Previously, we reported space–time clustering and seasonal variation in childhood central nervous system (CNS) tumours for the period 1954–1998. These previous studies provided evidence that infections may be involved in aetiology. To determine whether there were also localised spatial factors involved in aetiology we analysed the geographical distribution of CNS tumours in children aged 0–14 years using Manchester Children's Tumour Registry (MCTR) data for the period 1976–2000. Specifically, the Potthoff–Whittinghill test for spatial clustering was applied and Poisson regression was used to analyse the relationship between incidence rates and small-area population density, ethnic composition and deprivation index. No relationships were seen for all CNS tumours together and only a few for the subgroups. The previous findings of space–time clustering and seasonal variation, involving astrocytoma and ependymoma, together with the lack of spatial clustering and ecological relationships for these tumours provide evidence that astrocytoma and ependymoma may be associated with a highly mobile transient aetiological agent. An example of such an agent is an infection that occurs in mini-epidemics.

Keywords: Aetiology; Central nervous system tumour; Children; Clustering; Environment; Epidemiology; Infection; Small-area analysis

1. Introduction

The aetiology of childhood central nervous system (CNS) tumours remains uncertain. The only established causes are heritable syndromes, but these only account for a small number of cases [1]. We have recently reported space–time clustering among cases of CNS tumours included in the Manchester Children's Tumour Registry (MCTR) [2]. This was due to space–time clustering among cases of astrocytoma and ependymoma, but there was no space–time clustering among cases of medulloblastoma and other primitive neuroectodermal tumours (PNETs), nor among cases of "miscellaneous glioma" [2]. We have also reported seasonal variation in certain CNS tumours, including astrocytoma and ependymoma [2]. These findings are consistent with a role for infections in aetiology.

Descriptive epidemiological studies, including those on disease clustering and the relationship between incidence rates and area-based demographic variables are

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very useful in formulating aetiological hypotheses. Whilst there have been numerous clustering and ecological studies on childhood leukaemia, there have been very few similar studies on CNS tumours [3]. Increasing incidence, space–time clustering, spatial clustering and ecological relationships have been found for leukaemia, an infectious aetiology has been postulated and several mechanistic hypotheses have been suggested [4–6]. There has been a lack of plausible aetiological hypotheses for childhood CNS tumours.

To provide further insight into aetiology, we have examined the geographical distribution of CNS tumours for the same study area. Specifically, we have tested for spatial clustering, for spatial autocorrelation (the adjacency of areas with similarly high or low rates) and for ecological gradients.

The Manchester Children's Tumour Registry (MCTR) collects incidence data on all cancers in children, aged 0–14 years, from a defined geographical region of North-West England. Ascertainment has been estimated to be close to 100% [7]. The registry retains diagnostic specimens and re-review is undertaken periodically in line with improved knowledge about disease and technological advances. The MCTR thus provides a unique data-set for the investigation of incidence patterns over a wide geographical area and time-frame.

First, we have analysed the data for spatial clustering. Secondly, we have tested for spatial autocorrelation, i.e. we have tested for the adjacency of areas with similarly high or low rates. Finally, we have examined the data for ecological gradients by analysing the relationship between incidence rates and population density, measures of ethnic population composition and the level of deprivation, all at small-area (census ward) level. We have interpreted the geographical analyses in combination with the previously reported findings of space–time clustering and seasonal variation.

2. Patients and methods

Cases, aged 0–14 years, diagnosed between 1 January 1976 and 31 December 2000, registered with the MCTR and resident in the counties of Lancashire and Greater Manchester were included in the study. This time period was used, because appropriate census population counts and socio-demographic data were only consistently available from the 1981 census onwards. The classification scheme based on the international classification of diseases for oncology (ICD-O) second edition and revised to take account of developments in histopathology was used [8–10]. The diagnostic groups analysed comprised all CNS tumours (567 cases), all astrocytomas (229 cases), pilocytic astrocytomas (146 cases), other astrocytomas (83 cases), ependymomas (47 cases), astrocytomas plus ependymomas (276 cases), medulloblastomas (93 cases), other miscellaneous gliomas (79 cases) and miscellaneous specified CNS tumours (62 cases). The remaining groups had small numbers of cases and so were not considered for formal individual analysis, but were analysed as part of all CNS tumours (choroid plexus tumours, 29 cases; and miscellaneous unspecified CNS tumours, 15 cases).

Analyses were performed at the census ward level. The childhood population in the census wards ranged between 117 and 4194. During the study period, there were two national censuses. Two time periods (1976–1985 and 1986–2000) were considered for some analyses because: (i) small-area census population data were only available from the 1981 and 1991 censuses [11,12]; and (ii) they provided sufficiently long time periods to allow adequate case numbers for analyses, but not so long for population shifts to dilute any area-specific effects. This was confirmed by sensitivity analysis by repeating the analyses with the data from the years 1996–2000 omitted and which showed very similar results to the analyses for the full study period. It should be noted that there were some boundary changes at the ward level between the 1981 and 1991 censuses.

The reference address for all cases was the address at diagnosis. There were 519 wards involved in the 1981 census and 518 in the 1991 census. Cases were allocated to wards based on their address at diagnosis [13,14].

The full details of the statistical methods have been given elsewhere in [15]. The Potthoff–Whittinghill test [16–18] was used to test for spatial clustering at the ward level. The Smans test [19] was used to test for spatial autocorrelation at the district and ward levels, which would indicate adjacency of areas with high (or low) rates. Ward characteristics were derived from the small-area statistics of the censuses [11,12] and these included population density, ethnic composition, level of deprivation and urban–rural status. The Townsend score for deprivation at the ward level (and not the individual level) was calculated [20]. This is a combination of four census measures: unemployment, households without access to a car, home tenancy and household overcrowding. Wards were categorised as urban or rural using the Office for National Statistics (ONS) classification [21]. This is based on the predominant land use for the ward.

Area-based analyses were carried out. Statistical analyses (ecological regressions) were performed using Poisson regression. Continuous variables were cut into strata so that each stratum contained an (approximately) equal proportion of the childhood population. The following ward variables were cut into quintiles: population density, child population density, percentage white population, percentage Pakistani population, percentage Indian population (these were the three largest ethnic groups), the Townsend deprivation score and its components. As most wards were entirely urban, the

urban–rural score formed three groups, comprising approximately 60%, 20% and 20% of the childhood population, respectively.

A series of univariate analyses were carried out. For each quintile, the observed (O) and expected (E) numbers of cases were obtained, and the ratio O/E was calculated. A relative risk (RR) was calculated, for each quintile, by comparing the ratio O/E with the value of O/E for the first quintile (i.e. the 20% of the childhood population who resided in a ward that had the lowest value of the explanatory variable). The first quintile was assigned a RR of 1. Confidence intervals (CIs) were obtained. A test for linear trend was performed. Statistical significance was taken as $P < 0.05$ throughout the analyses.

3. Results

The observed numbers of cases by age group, time period, diagnostic group and gender are given in Table 1. The person–years at risk for the analyses are also presented.

3.1. All CNS tumours

There was no evidence for spatial clustering (P-values range from 0.10 to 0.67) or for spatial autocorrelation (P-values range from 0.25 to 0.66). Ecological analyses showed no statistically significant relationships (P-values range from 0.13 to 0.98) (Tables 2 and 3).

3.2. Astrocytoma

There was no evidence for spatial clustering (P-values range from 0.40 to 0.82) or for spatial autocorrelation (P-values range from 0.36 to 0.95). Poisson regression analyses showed no significant relationships between the incidence of astrocytoma and ecological variables (P-values for monotonic trends range from 0.13 to 0.97).

Further analysis by subgroup (pilocytic astrocytoma; other astrocytoma) was carried out. Again, this showed no evidence for spatial clustering (P-values range from 0.22 to 0.90) or for spatial autocorrelation (P-values range from 0.38 to 0.89). In addition, ecological analyses, by subgroup, showed no significant relationships (P-values for monotonic trends range from 0.07 to 0.96).

3.3. Ependymoma

There was no evidence for spatial clustering (P-values range from 0.27 to 0.74) or for spatial autocorrelation (P-values range from 0.19 to 0.61). Poisson regression analyses showed no significant relationships between the incidence of ependymoma and ecological variables (P-values for monotonic trends range from 0.24 to 0.98).

3.4. Astrocytoma and ependymoma

There was no evidence for spatial clustering (P-values range from 0.23 to 0.73) or for spatial autocorrelation (P-values range from 0.24 to 0.98). Poisson regression analyses showed no significant relationships between the incidence of astrocytoma and ependymoma and ecological variables (P-values for monotonic trends range from 0.25 to 0.90).

3.5. Other miscellaneous glioma

This group comprised 30 biopsied cases (eight malignant gliomas not otherwise specified (NOS), nine mixed gliomas, five subependymal giant cell astrocytomas, one

Table 1
Observed cases and person–years at risk by diagnostic group

	All CNS	Astrocytoma	Ependymoma	Other miscellaneous glioma	Medulloblastoma	Miscellaneous specified CNS	Person–years at risk
1976–1985							
0–4 years	73	21	13	5	13	6	2402260
5–9 years	83	33	5	14	23	7	2667820
10–14 years	81	37	6	10	17	9	3235580
Male	134	49	15	14	34	11	4263330
Female	103	42	9	15	19	11	4042330
Total	237	91	24	29	53	22	8305660
1986–2000							
0–4 years	121	41	12	18	17	12	4087665
5–9 years	116	54	8	20	18	7	3874350
10–14 years	93	43	3	12	5	21	3587340
Male	171	61	11	28	23	24	5911845
Female	159	77	12	22	17	16	5637510
Total	330	138	23	50	40	40	11549355

CNS, central nervous system.

Table 2
All CNS analyses: ward population density and ethnic mix ([1] data available for wards: 1976–2000; [2] data only available for wards: 1986–2000 [Quintile 1, lowest; Quintile 5, highest])

Quintile	Population density [1][a]	Childhood population density [1][b]	Percentage white [2][c]	Percentage Pakistani [2][d]	Percentage Indian [2][e]	Percentage rural [2][f]
1	RR = 1	RR = 1	RR = 1	RR = 1	RR = 1	RR = 1
2	RR = 1.04 (0.79–1.36)	RR = 1.00 (0.77–1.31)	RR = 1.06 (0.75–1.49)	RR = 1.13 (0.80–1.60)	RR = 1.10 (0.77–1.59)	
3	RR = 1.12 (0.86–1.46)	RR = 1.23 (0.96–1.59)	RR = 1.14 (0.82–1.60)	RR = 1.17 (0.83–1.65)	RR = 1.33 (0.93–1.89)	
4	RR = 1.38 (1.07–1.77)	RR = 1.20 (0.93–1.55)	RR = 1.05 (0.74–1.48)	RR = 1.17 (0.83–1.65)	RR = 1.39 (0.98–1.97)	RR = 1.21 (0.93–1.57)
5	RR = 0.88 (0.66–1.15)	RR = 0.87 (0.65–1.15)	RR = 0.94 (0.66–1.34)	RR = 1.03 (0.72–1.47)	RR = 1.22 (0.85–1.74)	RR = 0.80 (0.59–1.09)
Test for linear trend	$P = 0.75$	$P = 0.86$	$P = 0.76$	$P = 0.91$	$P = 0.13$	$P = 0.40$

RR, relative risk with 95% CLs in brackets.
[a] Quintile boundaries: 1 [5–1245]; 2 [1246–2158]; 3 [2158–3176]; 4 [3178–4356]; 5 [4367–10420] persons per square km.
[b] Quintile boundaries: 1 [1–251]; 2 [253–434]; 3 [437–653]; 4 [653–887]; 5 [894–3829] children per square km.
[c] Quintile boundaries: 1 [21.9–93.7]; 2 [93.8–97.6]; 3 [97.6–98.6]; 4 [98.6–99.2]; 5 [99.2–100] percentage of population.
[d] Quintile boundaries: 1 [0–0.05]; 2 [0.05–0.1]; 3 [0.1–0.4]; 4 [0.4–1.9]; 5 [2.0–50.4] percentage of population.
[e] Quintile boundaries: 1 [0–0.1]; 2 [0.1–0.2]; 3 [0.2–0.4]; 4 [0.4–1.0]; 5 [1.0–48.2] percentage of population.
[f] Quintile boundaries: 1 [all urban]; 4 [3.0–6.7]; 5 [7.1–100] percentage of "rural" enumeration districts.

Table 3
All CNS analyses for components of deprivation (data available for wards: 1976–2000) [Quintile 1, lowest; Quintile 5, highest]

Quintile	Townsend score[a]	Unemployment[b]	Households without access to a car[c]	Tenancy[d]	Household overcrowding[e]
1	RR = 1	RR = 1	RR = 1	RR = 1	RR = 1
2	RR = 0.99 (0.76–1.28)	RR = 1.17 (0.90–1.52)	RR = 1.17 (0.90–1.51)	RR = 1.00 (0.77–1.30)	RR = 1.15 (0.89–1.49)
3	RR = 1.09 (0.84–1.40)	RR = 1.24 (0.95–1.61)	RR = 1.02 (0.79–1.34)	RR = 1.07 (0.83–1.39)	RR = 0.99 (0.76–1.30)
4	RR = 0.83 (0.63–1.09)	RR = 0.91 (0.69–1.21)	RR = 0.87 (0.66–1.15)	RR = 0.91 (0.69–1.19)	RR = 1.11 (0.85–1.44)
5	RR = 1.08 (0.84–1.39)	RR = 1.21 (0.93–1.57)	RR = 1.15 (0.89–1.49)	RR = 1.10 (0.85–1.42)	RR = 0.98 (0.75–1.28)
Test for linear trend	$P = 0.98$	$P = 0.61$	$P = 0.95$	$P = 0.73$	$P = 0.78$

RR, relative risk with 95% CLs in brackets.
[a] Quintile boundaries: 1976–1985 1 [−5.7 to −2.4]; 2 [−2.3 to −0.7]; 3 [−0.7 to 1.5]; 4 [1.5 to 4.0]; 5 [4.1 to 13.1], 1986–2000 1 [−5.0 to −2.3]; 2 [−2.3 to −0.7]; 3 [−0.7 to 1.3]; 4 [1.3 to 4.3]; 5 [4.3 to 14.7].
[b] Quintile boundaries: 1976–1985 1 [1.2 to 7.1]; 2 [7.1 to 9.5]; 3 [9.5 to 12.1]; 4 [12.1 to 16.3]; 5 [16.6 to 33.5] percent, 1986–2000 1 [1.8 to 6.0]; 2 [6.0 to 8.2]; 3 [8.2 to 10.8]; 4 [10.8 to 16.7]; 5 [16.7 to 39.2] percent.
[c] Quintile boundaries: 1976–1985 1 [9.0 to 30.7]; 2 [30.7 to 40.8]; 3 [41.0 to 49.3]; 4 [49.4 to 58.8]; 5 [58.9 to 86.0] percent, 1986–2000 1 [4.6 to 25.0]; 2 [25.1 to 34.1]; 3 [34.2 to 42.2]; 4 [42.3 to 51.9]; 5 [51.9 to 81.4] percent.
[d] Quintile boundaries: 1976–1985 1 [2.8 to 20.3]; 2 [20.3 to 30.3]; 3 [30.3 to 39.8]; 4 [39.8 to 55.0]; 5 [55.2 to 99.5] percent, 1986–2000 1 [1.7 to 16.1]; 2 [16.1 to 24.6]; 3 [24.8 to 33.7]; 4 [33.8 to 48.4]; 5 [48.5 to 97.9] percent.
[e] Quintile boundaries: 1976–1985 1 [0.2 to 1.9]; 2 [1.9 to 2.8]; 3 [2.8 to 3.8]; 4 [3.8 to 5.1]; 5 [5.1 to 21.8] percent, 1986–2000 1 [0 to 1.0]; 2 [1.0 to 1.5]; 3 [1.5 to 2.1]; 4 [2.1 to 2.9]; 5 [3.0 to 21.0] percent.

astroblastoma, four oligodendroglioma NOS, three anaplastic oligodendroglioma) and 49 unbiopsied cases classified as malignant glioma NOS. There was no evidence for spatial clustering (*P*-values range from 0.19 to 0.35) nor for spatial autocorrelation (*P*-values range from 0.10 to 0.16). Ecological analyses showed statistically significant monotonic relationships for more densely child-populated areas (*P*-value for monotonic trend is 0.05, *P*-value for quadratic effect is 0.005), for more deprived areas (*P*-value for monotonic trend is 0.02, *P*-value for quadratic effect is 0.12), for areas with smaller percentages of whites (*P* for monotonic trend is 0.04, *P* for quadratic effect is 0.75). However, further analysis by glioma, NOS (57 cases) and the remainder (22 cases) showed no significant relationships for glioma, NOS. There were some significant relationships amongst the remainder (22 cases), but this was a small and heterogeneous group.

3.6. Medulloblastoma

There was evidence for spatial clustering for the second time period, 1985–2000 ($P = 0.03$), but not the first time period, 1976–1985 ($P = 0.47$). There was no evidence for spatial autocorrelation (*P*-values range from

0.14 to 0.26). Poisson regression analyses showed no significant relationships between the incidence of medulloblastoma and ecological variables (*P*-values for monotonic trends range from 0.15 to 0.86).

3.7. Miscellaneous specified CNS tumours

There was no evidence for spatial clustering (*P*-values range from 0.22 to 0.73) or for spatial autocorrelation (*P*-values range from 0.13 to 0.42). Poisson regression analyses showed no significant relationships between the incidence of miscellaneous specified CNS tumours and ecological variables (*P*-values for monotonic trends range from 0.10 to 0.97).

4. Discussion

This analysis completes a set of analyses of childhood CNS tumours from North-West England and thus is important in interpreting the data and formulating aetiological hypotheses. This study has only been made possible by the availability of high-quality and consistent population-based diagnostic and residential address data. As ascertainment is close to 100%, there is no reason to suspect that there is any artifactual bias by the small-area of diagnosis.

There are two main types of clustering: space–time clustering and spatial clustering. Space–time clustering may be described as the irregular grouping of cases of any disease simultaneously in space and time and may arise, for example, whenever there are a small number of locations with greatly increased incidence at short (but distinct) periods of time, or, whenever there are a large number of limited time periods with moderately increased incidence at limited locations. Spatial clustering is defined as the irregular grouping of cases of any disease in space. Such an irregular distribution is a general phenomenon and is not confined to one specific small area. These irregularities could arise because there are small numbers of areas with greatly increased incidence or a large number of areas with moderately increased incidence. There are a number of possible outcomes that we may observe and which provide differing aetiological clues.

(1) Space–time clustering, seasonal variation, spatial clustering and ecological gradients for the same data-set would provide evidence of an environmental agent which occurs in very localised areas which have specific socio-demographic characteristics. An example, which may lead to such a situation, is infectious episodes occurring in a number of localised areas of very high population mixing and which have high socio-economic status. The population mixing and high area-based socio-economic status may be due to the presence of a highly mobile professional population.
(2) Space–time clustering, seasonal variation and spatial clustering for the same data-set in the absence of ecological gradients would provide evidence of an environmental agent which occurs in very localised areas, but which does not have consistent socio-demographic characteristics. An example is infectious episodes occurring in a number of localised areas of very high population mixing, and which have variable socio-economic status, such as population mixing due to transient tourist populations.
(3) Space–time clustering, seasonal variation and ecological gradients for the same data-set, but no spatial clustering would provide evidence of an environmental agent which occurs in areas which have specific socio-demographic characteristics. An example is infectious episodes occurring in areas of high socio-economic status.
(4) Space–time clustering and seasonal variation only would provide evidence of a highly mobile transient aetiological agent, such as an infection that occurs in mini-epidemics.

We have previously found space–time clustering among cases of CNS tumours and specifically among cases of astrocytoma and ependymoma for the same data-set [2]. We have also identified seasonal variation among cases of astrocytoma, ependymoma and craniopharyngioma for the same data-set [2]. These previous findings provide evidence for the involvement of infections in the aetiology of astrocytoma and ependymoma. The new findings from the present study show an absence of spatial clustering and any ecological correlation between incidence rates and socio-demographic variables. This pattern is consistent with outcome (4) described above.

Several methodological points should be noted. The ethnic composition of the ward is not necessarily related to characteristics of individual cases and must only be used as an ecological measurement. Similarly, population density and the deprivation scores are ward-based and are not individual measures. Caution should be exercised when using such grouped data to make inferences about individuals. A large number of statistical tests have been performed, albeit on correlated measures. The small number of statistically significant results could have been expected to occur by chance alone.

The overall results for the CNS tumours contrast with findings for leukaemia. Various studies, from the United Kingdom (UK) and elsewhere, have found that childhood leukaemia has increased in incidence, exhibits space–time clustering, spatial clustering and has been noted to occur in excess in areas with high population mixing [3]. Three hypotheses [4–6] have been proposed to explain the pattern of occurrence for leukaemia

including delayed exposure to common infection and unusual population mixing.

A smaller study of childhood CNS tumours from Yorkshire, UK for the period 1974–1995, which was based on 455 cases, did not find any association between the incidence of CNS tumours and ward-based ecological measures [22]. These findings were largely confirmed in North-West England. However, it should be noted that the Yorkshire study used an earlier diagnostic classification scheme [23]. In addition, a full set of analyses has not, so far, been done on the Yorkshire data-set.

Space–time clustering has also been identified in cases of ALL in the MCTR region of North-West England [24,25]. Further, we found no evidence of spatial clustering and only one significant ecological relationship (population density) for ALL [26]. A number of other studies have found both space–time and spatial clustering for ALL, but not for CNS tumours [27]. We infer that the geographical pattern of incidence of the CNS tumours, especially astrocytoma and ependymoma, is akin to the pattern observed for ALL. Such a pattern of space–time clustering without spatial clustering or marked ecological gradients is suggestive of a highly mobile aetiological mechanism, such as numerous mini-epidemics of an infectious agent or agents throughout the study region.

The finding of a temporal increase for CNS tumours from North-West England [28] is noteworthy, since a temporal increase has also been found for ALL [29,30].

However, the increase applied to all sub-groups, except ependymoma, and thus was not as specific as the finding for ALL which was confined to cases of ALL in the childhood peak [29].

In summary, we have found no evidence for spatial clustering or spatial autocorrelation among the CNS tumours or any sub-groups. In addition, we have found no significant ecological relationships (apart from the heterogeneous group ''other miscellaneous glioma''). These new results for astrocytoma and ependymoma, taken together with the previous findings of space–time clustering and seasonal variation would point to a highly mobile and transient aetiological agent. An obvious candidate would be an infection that presents in mini-epidemics. Further research is needed to provide better insight into the precise aetiological mechanism for astrocytoma and ependymoma.

Conflict of interest statement

None declared.

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