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Space–time clustering patterns of gliomas in the Netherlands suggest an infectious aetiology

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Abstract

To test the hypothesis that infectious exposures may be involved in glioma aetiology, we have analysed space–time clustering and seasonal variation using population-based data from the South of the Netherlands between 1983 and 2001. Knox tests for space–time interactions between cases were applied, with spatial coordinates of the addresses at time of diagnosis, and with distance to the *N*th nearest neighbour. Data were also analysed by a second order procedure based on *K*-functions. Tests for heterogeneity and Edwards' test for sinusoidal variation were applied to examine seasonal variation of incidence. There was statistically significant space–time clustering in the Eastern, but not in the Western part of the region. Clustering was only present in adults, particularly in less densely populated areas. There was no evidence for seasonal variation. The results support a role for infectious exposures in glioma aetiology that may act preferentially in certain geographical areas.

Keywords: Aetiology; Glioma; Infection; Seasonal variation; Space–time clustering

1. Introduction

Gliomas are the most common primary brain tumours in children and adults. Thus far only ionising radiation has been established as an aetiological factor [1,2], and few genetic syndromes exist which predispose to glioma [3,4]. These factors however can only explain a small minority of cases, whilst the evidence for many other proposed risk factors is inconclusive [5]. A role for infection in the aetiology of glioma has been suggested. Certain viruses, including polyomaviruses, JC virus, BK virus and simian virus 40 (SV40) have been considered as possible aetiological agents but the findings have been inconsistent [6,7]. If infectious exposures are involved, the distribution of cases may exhibit space–time clustering. This would happen if an aetiologically linked infectious exposure occurred in 'mini-epidemics' and would be detected when the lag time from exposure to diagnosis is short or relatively constant.

Space–time clustering is said to occur when excess numbers of cases are observed within small geographical locations at limited periods of time that cannot be

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explained in terms of general excesses in those locations or at those times. The presence of seasonal variation would also provide indirect evidence for an aetiology involving infections that exhibited seasonal epidemicity. Examples of infections that display such epidemicity include the common cold, influenza and measles. Space–time clustering has been examined previously for childhood brain tumours using data from the Manchester Children's Tumour Registry (MCTR). Statistically significant evidence for space–time clustering was found, particularly for astrocytoma and ependymoma, with an excess of patients born in Autumn or Winter [8]. However, in a study investigating childhood astrocytoma in Sweden, space–time clustering could not be shown [9]. To date, studies examining space–time clustering in adult glioma have not been published.

In the present study, we investigated space–time clustering and seasonal variation in adult and childhood glioma to assess the possibility of an infectious aetiology, using population-based data from cancer registries in the South of the Netherlands.

2. Patients and methods

The Eindhoven Cancer Registry within the framework of the Comprehensive Cancer Centre South and the Cancer Registry of Rotterdam registered all glioma patients in North Brabant. This province in the South of the Netherlands has 2.3 million inhabitants and covers an area of nearly 5000 km^2. The cancer registries in the Netherlands are characterised by high quality incidence data and near complete ascertainment [10,11]. Data were available for 1983–2001 for the Eastern part and 1989–2001 for the Western part of the province (the Eastern and Western parts are contiguous). To avoid any methodological bias, the Eastern and Western areas were analysed separately. All cases diagnosed with a central nervous system glioma were analysed.

For each case of glioma, geographical coordinates were allocated to the postcode of the address at the time of diagnosis. The geographical coordinates were obtained using the Dutch Triangular System (Rijksdriehoeksmeting; www.rdnap.nl), the most widely used geographical reference system in the Netherlands. This enabled spatial referencing of the Easting and Northing coordinates to within 0.1 km of the actual address. For 7% of the cases in the total area of North Brabant and for all of those in a small region in the most Western part of the Western area, only partial postcodes (4 digits) were available, locating cases to the level of neighbourhoods and small municipalities. For these cases a random coordinate was used within the specified area. Sensitivity analyses were performed by repeating the analyses with another two different random coordinates. This created three data sets for analysis.

The following aetiological hypotheses were tested: (i) a primary factor influencing geographical or temporal heterogeneity of incidence of gliomas is related to exposure to an infectious or other similarly occurring environmental agent relatively close to disease onset; and (ii) geographical or temporal heterogeneity of incidence of gliomas is modulated by differences in patterns of exposure related to level of population density. Space–time interactions based on time and place of diagnosis were tested.

Knox space–time clustering tests were applied to the data with thresholds fixed, a priori, as: close in space, less than 5 km; and close in time, less than one year apart [12]. These limits are arbitrary, but have been used in a number of studies of space–time clustering of childhood cancers from North West England [8,13–16]. Furthermore, this problem is overcome by using the *K*-function method (see below). In the Knox test, a pair of cases is regarded as being in 'close proximity' if they are both diagnosed at addresses that are simultaneously close in space and at times that are close. The number of pairs of cases observed to be in close proximity was obtained (O) and the number of pairs of cases expected to be in close proximity was calculated (E). If O exceeded E there was space–time clustering and statistical tests were used to determine whether this excess was statistically significant. The magnitude of the excess (or deficit) was estimated by calculating $S = ((O - E)/E) \times 100$. To adjust for the effect of different population densities, the tests were repeated replacing geographical distance thresholds by distance to the Nth nearest neighbour, using all locations of all the cases in the data set. N was chosen such that the mean distance was 5 km and was found to be $N = 30$.

Two problems are apparent with the Knox test. First, boundary problems may be important since it can be impossible, or less probable, for some cases to be close in one dimension to other cases. The second problem concerns the arbitrariness of the thresholds chosen. A simplification of a second order procedure based on *K*-functions was used in the present analyses to overcome the problem of arbitrary boundaries [17]. This procedure involved a set of 225 Knox-type calculations where the boundaries changed over a pre-specified set of values (for close times, $t = 0.1, 0.2, \ldots, 1.5$ years and for close in space, $s = 0.5, 1, 1.5, \ldots, 7.5$ km). Statistical significance was assessed by simulation. Nearest neighbour (NN) approaches were also used (analogous to those described in relation to classical Knox tests).

Two age-groups were studied: 0–14, 15+ years. These age-groups were selected to attempt to differentiate between the potential effect of infectious exposures for children and older cases. For younger cases, genetic predisposition would be predicted to be an important component of aetiology in combination with the triggering infectious exposure, whilst for older cases the main

aetiological factor would be predicted to be the infectious exposure that precipitates the onset of the tumour.

To test the effect of the opportunity for exposure to infectious agents, via closer person to person contact, analyses were performed for two levels of population density. Addresses were classified as being located in a more densely populated area, or being located in a less densely populated area. For addresses at time of diagnosis the median distance for the 30th nearest neighbour was found. Diagnosis locations, whose 30th nearest neighbour was less than the median distance, were classified in the 'more densely populated' category. Diagnosis locations, whose 30th nearest neighbour was greater than the median distance, were classified in the 'less densely populated' category. Analysis was undertaken by considering pairs of cases including at least one case from the 'more densely populated' category and pairs of cases including at least one case from the 'less densely populated' category. The observed and expected numbers of pairs of cases were calculated where: (i) both cases came from a 'more densely populated' area; (ii) both cases came from a 'less densely populated' area; and (iii) one case came from a 'more densely populated area' and the other case came from a 'less densely populated' area. It should be noted that these analyses (especially the analyses of clustering pairs including at least one case from the 'less densely populated' category) are potentially subject to a strong diluting influence from edge effects since neither the 'more densely populated' areas nor the 'less densely populated' areas form a single spatially contiguous zone.

Of the three data sets, for all the analyses, the most conservative results in terms of *P*-value and for the Knox test, strength (*S*) within *P*-value are presented in tables. Statistical significance was indicated if $P < 0.05$, using at least 2 of the 4 methods (the geographical or NN versions of the Knox test and the *K*-function method), and including a NN threshold version.

To examine seasonal variation the cases were examined for monthly variation in dates of birth and diagnosis using: (i) a χ^2 test for heterogeneity, and (ii) Edwards' test for sinusoidal variation [18]. The overall distribution of months of birth and diagnosis of all cancer patients registered by the Eindhoven Cancer Registry were used to correct the underlying variation in birth and diagnosis dates.

3. Results

For the province of North Brabant there were 1545 cases of glioma diagnosed between 1983 and 2001 (59.5% males, median age at diagnosis 52 years, range 0–92). There were 37 cases of pilocytic astrocytoma, 1064 cases of other astrocytoma, 131 cases of oligodendroglioma, 79 cases of ependymoma and 234 cases of other glioma including glioma not otherwise specified (NOS) and clinically diagnosed tumours. There were 124 cases of glioma in the most Western part of the Western area with only partial postcodes available.

There was statistically significant space–time clustering for cases from the Eastern, but not for cases from the Western part of the province ($P < 0.05$ using at least 2 methods and including a NN threshold version; Table 1). Statistically significant space–time clustering was found for cases of glioma aged over 15 years ($P < 0.05$ using at least 2 methods and including a NN threshold version), but not for children aged 0–14 years. Again this was apparent for cases from the East but not the West (Table 2). There was also no cross-clustering between the older (aged 15+ years) and younger cases (aged 0–14 years). When testing

Table 1
Space–time clustering tests for glioma cases (all ages) in the South of the Netherlands and diagnosed during the period 1983–2001, analysed by area and time period

Area and time period (number of cases)	Knox test (observed space–time pairs[a], expected space–time pairs, strength[b], *P*-value[c])		*K*-function analysis[f] (*P*-value[g])	
	Geographical distance[d]	NN threshold[e]	Geographical distance[h]	NN threshold[i]
East 1983–2001 (752 cases)	$O = 2550$; $E = 2482.9$ $S = 2.7\%$; $P = 0.09$	$O = 1659$; $E = 1555$ $S = 6.7\%$; $P = 0.005$	$P = 0.14$	$P = 0.01$
West 1989–2001 (793 cases)	$O = 2851$; $E = 2784.8$ $S = 2.4\%$; $P = 0.11$	$O = 2411$; $E = 2366$ $S = 1.9\%$; $P = 0.18$	$P = 0.34$	$P = 0.32$

[a] Cases are close in time if dates of diagnosis differ by less than 1 year.
[b] Strength (S) = {(Observed − Expected)/Expected} × 100 counts of pairs which are close in time and space.
[c] 1-sided *P*-value derived from the Poisson distribution.
[d] When using geographical distance cases are close in space if their locations are <5 km apart.
[e] When using nearest neighbour (NN) thresholds cases are close in space if the locations of one (or both) is nearer than the other's 30th NN in the total data set.
[f] Cases are close in time if dates differ by $<t$, where t is in the range 1–18 months.
[g] *P*-value obtained by simulation (999 runs) with dates of diagnosis randomly re-allocated to the cases in the analysis.
[h] Cases are close in space if distances between their locations differ by $<s$, where s is in the range 0.5–7.5 km.
[i] 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 23–37.

Table 2
Space–time clustering tests for glioma cases in the South of the Netherlands and diagnosed during the period 1983–2001, analysed by age-group, area and time period

Age-group, area and time period (number of cases)		Knox test (observed space–time pairs[a], expected space–time pairs, strength[b], *P*-value[c])		*K*-function analysis[f] (*P*-value[g])	
		Geographical distance[d]	NN threshold[e]	Geographical distance[h]	NN threshold[i]
East, 1983–2001	Age 0–14, (56)	$O = 8$; $E = 10.5$ $S = -23.5\%$; $P = 0.72$	$O = 6$; $E = 8.6$ $S = -29.9\%$; $P = 0.75$	$P = 0.94$	$P = 0.89$
	Age 15+, (696)	$O = 2239$; $E = 2161.2$ $S = 3.6\%$; $P = 0.05$	$O = 1440$; $E = 1335.6$ $S = 7.8\%$; $P = 0.003$	$P = 0.06$	$P = 0.003$
West, 1989–2001	Age 0–14, (45)	$O = 9$; $E = 10$ $S = -9.6\%$; $P = 0.54$	$O = 4$; $E = 7.8$ $S = -48.5\%$; $P = 0.89$	$P = 0.52$	$P = 0.79$
	Age 15+, (748)	$O = 2543$; $E = 2493.6$ $S = 2.0\%$; $P = 0.16$	$O = 2162$; $E = 2120.3$ $S = 2.0\%$; $P = 0.19$	$P = 0.44$	$P = 0.33$

[a] Cases are close in time if dates of diagnosis differ by less than 1 year.
[b] Strength (S) = {(Observed − Expected)/Expected} × 100 counts of pairs which are close in time and space.
[c] 1-sided *P*-value derived from the Poisson distribution.
[d] When using geographical distance cases are close in space if their locations are <5 km apart.
[e] When using nearest neighbour (NN) thresholds cases are close in space if the locations of one (or both) is nearer than the other's 30th NN in the total data set.
[f] Cases are close in time if dates differ by $<t$, where t is in the range 1–18 months.
[g] *P*-value obtained by simulation (999 runs) with dates of diagnosis randomly re-allocated to the cases in the analysis.
[h] Cases are close in space if distances between their locations differ by $<s$, where s is in the range 0.5–7.5 km.
[i] 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 23–37.

for population density there was statistically significant space–time clustering involving cases from 'less' densely populated areas in the East but not the West (Table 3). Finally, there was no evidence of seasonal variation within both age groups using either the χ^2 test for heterogeneity or Edwards' test for sinusoidal variation (data not shown).

4. Discussion

To our knowledge, we are the first to apply formal statistical methods on population-based incidence data to study space–time clustering in adult glioma. Space–time clustering based on time and place of diagnosis was found. Clustering was only present in adults (aged

Table 3
Space–time clustering tests for glioma cases in the South of the Netherlands and diagnosed during the period 1983–2001, analysed by population density, area and time period

Population density, area and time period		Knox test (observed space–time pairs[a], expected space–time pairs, strength[b], *P*-value[c])		*K*-function analysis[f] (*P*-value[g])	
		Geographical distance[d]	NN threshold[e]	Geographical distance[h]	NN threshold[i]
East, 1983–2001	MDP[j]	$O = 2221$; $E = 2172.3$ $S = 2.2\%$; $P = 0.15$	$O = 1039$; $E = 1002.9$ $S = 3.6\%$; $P = 0.13$	$P = 0.19$	$P = 0.14$
	LDP[k]	$O = 463$; $E = 444.3$ $S = 4.2\%$; $P = 0.19$	$O = 823$; $E = 751.1$ $S = 9.6\%$; $P = 0.005$	$P = 0.25$	$P = 0.02$
West, 1989–2001	MDP[j]	$O = 2385$; $E = 2335.8$ $S = 2.1\%$; $P = 0.16$	$O = 1486$; $E = 1459.1$ $S = 1.8\%$; $P = 0.24$	$P = 0.37$	$P = 0.49$
	LDP[k]	$O = 791$; $E = 786.0$ $S = 0.6\%$; $P = 0.43$	$O = 1370$; $E = 1362.9$ $S = 0.5\%$; $P = 0.43$	$P = 0.57$	$P = 0.52$

[a] Cases are close in time if dates of diagnosis differ by less than 1 year.
[b] Strength (S) = {(Observed − Expected)/Expected} × 100 counts of pairs which are close in time and space.
[c] 1-sided *P*-value derived from the Poisson distribution.
[d] When using geographical distance cases are close in space if their locations are <5 km apart.
[e] When using nearest neighbour (NN) thresholds cases are close in space if the locations of one (or both) is nearer than the other's 30th NN in the total data set.
[f] Cases are close in time if dates differ by $<t$, where t is in the range 1–18 months.
[g] *P*-value obtained by simulation (999 runs) with dates of diagnosis randomly re-allocated to the cases in the analysis.
[h] Cases are close in space if distances between their locations differ by $<s$, where s is in the range 0.5–7.5 km.
[i] 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 23–37.
[j] $\geqslant 1$ case from a more densely populated (MDP) area.
[k] $\geqslant 1$ case from a less densely populated (LDP) area.

15+ years) from the Eastern part of the province, particularly in less densely populated areas. Conversely, there was no evidence for space–time clustering amongst children (aged 0–14 years). Seasonal variation in incidence of glioma could not be shown.

The cancer incidence data from the Comprehensive Cancer Centres in the Netherlands are characterised by high quality and near complete ascertainment [10,11]. Pathological diagnoses were derived from different sources including the Dutch computerised nationwide registry of histo- and cytopathology (PALGA) and the Dutch Medical Register (LMR). Methods for data collection were the same in the Western and the Eastern areas, and have not changed since 1983. For all cases, the address at diagnosis was recorded, as well as the last known address which is regularly updated using municipal records. For 24 cases only, these addresses were different indicating a low possibility of bias due to migration. Otherwise, migration may lead to either an underestimation or overestimation of the strength of clustering.

Unfortunately it was not possible to analyse the data as one entity because cases were not consistently available for the entire study area since 1983. Thus separate analyses were undertaken. However, comparison between the East and the West was possible. There is no method for combining the results of these separate analyses as the effect of time and space boundaries would invalidate such an attempt.

The problem of cases with only partially known postcodes was solved by sensitivity analyses using different data sets with random coordinates within the specified area. The analyses were performed using rigorous statistical methods. The many tests involved in this study raised the possibility of a multiple testing problem. Although analyses were performed following prior hypotheses and although only the most conservative results were used, the results still have to be interpreted with care. The number of cases in the younger age group (0–14 years) was small compared with the study from North West England [8], so there was much less power in the present study to be able to detect clustering in this age group.

It is possible that the methodology may be biased if there are certain differential population changes during the time period, especially when the population grows or declines at different rates in different areas of the study region. A method to deal with this particular type of problem has been proposed [19], but it would not be possible to implement this procedure on the current data set, because it requires small area population data by month that are not available. However, it must be stressed that the current analyses provide a description of the space–time clustering patterns in the data, whether real or artifactual. Additionally, variations in population growth are not thought to be important in the current data set.

The pattern of space–time clustering found in this study is consistent with an exposure occurring at a relatively short time period before onset of the disease. It is likely that this exposure is more important among those aged over 15 years. The nature of space–time interaction implies an exposure emerging at many points in both place and time. Therefore, more sustained exposures which are geographically fixed and present for long periods of time (e.g., power lines, environmental pollution or industry) can be excluded. The pattern is however more consistent with an infectious agent. Since there was only space–time clustering in the Eastern part of the province, this agent is likely to act in limited geographical areas, without spreading to other regions. This would imply that this agent does not have the capability for rapid spreading, or that it is linked to, e.g., industries or environments that are more common in the East. The more marked clustering in less densely populated areas might indicate that the aetiological agent is more prevalent in these environments. We however do not know of any common industry or environment that is typical for the Eastern part of the province of North Brabant.

Evidence for the involvement of infections in the aetiology of glioma comes primarily from studies in experimental animals and from the isolation of several viruses from human tumour material. The importance of these findings to glioma aetiology is uncertain. Few epidemiological studies addressing the role of infections have been published, which may also indicate unpublished negative results. For adult glioma, antibody titres to *Toxoplasma gondii* were linked to astrocytoma [20], although an association could not be confirmed by others [21]. For childhood glioma, four epidemiological studies suggested an infectious component to aetiology [22–25], whilst another case–control study found no such relations [26].

No studies concerning space–time clustering in adults have been published thus far. Therefore comparisons can only be made for childhood brain tumours. In the present study, no clustering was detected for the youngest age category. Also, no space–time clustering was found in childhood astrocytoma in Sweden [9]. Space–time clustering was however reported for childhood brain tumours using population-based data from the Manchester Children's Tumour Registry (MCTR) [8]. Strong evidence for space–time clustering was found for astrocytoma, ependymoma and all glioma combined. The present study contained far fewer cases of childhood glioma than the MCTR study, whilst the Swedish study used a different methodology. It is possible that the lack of space–time clustering in the present study is due to insufficient power to detect such an effect.

We found no evidence for seasonal variation in glioma incidence. In earlier studies however, seasonal variation was observed for childhood astrocytoma and ependymoma [8], for all childhood brain tumours [27],

and for adult glioma [28]. All studies reported excesses in incidence for late autumn and winter births. The first two studies concerned childhood glioma and brain tumours only, probably explaining most of the discrepancies with the present study in which there was insufficient power owing to a lack of childhood cases. The third study investigating adult glioma used a different methodology. Furthermore, we used a robust method of adjusting variations in birth and diagnosis date with the overall distribution of months of birth and diagnosis for all cancer patients registered by the cancer registry.

In summary, space–time clustering was found for cases of glioma from the Eastern part of the province, but only for adults aged >15 years. The results are consistent with an infectious agent, mainly acting in limited, less densely populated geographical areas without spreading to other regions. It is difficult to draw any firm conclusions concerning the childhood cases (aged 0–14 years), due to small numbers.

It is not clear whether there are one or more candidate infections or whether infectious agents in general act as a tumour promoter. Further research should include both epidemiological and laboratory investigations. An ecological investigation could relate incidence rates to levels of deprivation and studies of spatial clustering could determine if there are small areas with sustained high incidence. Laboratory studies might examine differences in the occurrence of specific putative agents between 'clustering' and 'non-clustering' cases.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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