Time-Space Clustering among Cases of Burkitt’s Tumor¹

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Summary

Although time-space clustering seems to be a prominent feature of Burkitt’s tumor in the West Nile District of Uganda, the findings have yet to be confirmed elsewhere in Africa. Evidence outside Africa is limited to anecdotal accounts of three individual clusters. Two involve pairs of cases in unrelated persons sharing no unusual epidemiological features, while the third concerns simultaneous Burkitt’s tumor in sibs.

BT³ in Africa

Time-space clustering has been described as a particular feature of BT in Africa. The finding is remarkable since, with the possible exception of Hodgkin’s disease and childhood acute leukemia, no other forms of cancer exhibit such an epidemiological property. Evidence rests largely on the 1967 report by Pike et al. (8), which demonstrated time-space clustering in the West Nile District of Uganda. The study encompassed all confirmed cases diagnosed from 1961 through 1965 (36 cases). Time-space patterns were assessed by 2 methods of statistical analysis: (a) the Knox approach (5), which examines the joint time-space separation of all possible case pairs, and (b) the David-Barton approach (2), which establishes time clusters and then considers the spatial separation of cases within individual time clusters. With the use of time intervals ranging from 30 to 360 days and space intervals from 2 to 40 km, both methods produced statistical evidence of clustering. The clustering observed, however, seemed mostly to involve large space intervals, beginning with 10 km. Larger intervals were not tested and relatively few case pairs fell into interval categories of 5 km or less. The results suggest a general drift in case occurrence over time from 1 geographic region to another, a picture that invites comparisons with epidemic infection where disease shifts from place to place as local immunity patterns change. Possibly, the drift observed may only reflect underlying shifts in population. However, information from indirect sources suggests that this is not the case (8, 10).

Further data from the West Nile District through 1967 (29 additional cases) have supported the concept of drift in case occurrence or coarse time-space clustering (10). As before, significant clustering was seen only at relatively large space intervals, none less than 5 to 6 km. However, the findings have yet to be confirmed in other parts of Africa. Mentioned, but not described in detail, are statistical studies in the region surrounding Kampala, Uganda (East and West Mengo districts), where no evidence of clustering among cases of BT at any time or space interval seems to have been found (10). Conceivably, these negative results may reflect the confounding effect of increased population mobility in relatively developed areas; if one expects place of residence to be an adequate indication of where disease is contracted, the picture can be obscured only as mobility increases and migration become more commonplace. On the other hand, the negative findings near Kampala may be an indication that the clustering seen in the West Nile District is artificial.

Other data suggesting that cases of BT in Africa may come in clusters consist purely of anecdotal accounts of individual clusters. The interpretation of such accounts is always open to question, although the rarer the disease, the stronger the intuitive appeal; such accounts may also carry more weight if the cases involved display unusual epidemiological associations other than mere time-space clustering. In Africa there have now been, to our knowledge, 3 references to individual clusters of BT cases, all 3 in Uganda. One is only sketchily described, 5 cases over a 2-year period in the village of Ahiba in the West Nile District (8). Of the other 2, 1 consisted of 15 cases dispersed over a 150- to 200-sq km area near Mount Wati in the West Nile District during the 7-year period 1961 to 1967 (10). Eleven of the 15 cases occurred during the last 2 years of that time period. The 3rd cluster occurred in Bwamba County, 7 cases over the 27 months from October 1966 through December 1968, 5 cases occurring in the last 6 months of that time period (7). Again, the area encompassed by the cluster was relatively large, approximately 150 sq km.

In none of these 3 clusters, with 1 exception, were any unusual epidemiological associations found among cases, other than relative time-space closeness. The exception involved 2 Bwamba County cases that occurred 5 months apart in sibs living in the same house: a 3-year-old girl with onset in July 1968, and a 9-year-old boy with onset in December 1968. While such a situation may well reflect genetic influences, the fact that the 2 cases occurred simultaneously in sibs of different ages favors a shared environmental etiology. Conceivably, familial situations such as this may be evidence of discrete time-space cluster-

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² Presented by.
³ The abbreviation used is: BT, Burkitt’s tumor.
ing. While there seems to be no general indication that BT tends to be familial, at least 3 other multiple-case family situations are recorded in the literature, 2 in Africa and 1 in the United States. Two of these 3 involve cases diagnosed close together in time, while information regarding data of case occurrence is not given for the 3rd. Of the 2 African family situations, 1 concerned 2 first cousins living in the same housing complex in Uganda with clinical onset less than 2 months apart (7). In the other, 2 sisters in Kenya were affected at unspecified dates and places (1). The 3rd situation took place in the United States and is described below.

**BT in the United States**

Outside Africa, evidence suggestive of time-space clustering among BT cases has only recently been advanced. This may well reflect the fact that the disease is extremely rare outside central Africa and parts of New Guinea and that its recognition, in the United States at least, is still only a recent phenomenon. In our registry of leukemia and lymphoma cases among residents of the metropolitan Atlanta, Ga., area, for instance, we have recorded only 3 cases in the past 5 years. Of these cases, 2 were under age 15, an average annual incidence of about 0.1 case/100,000 in this age group. In contrast, in Ibadan, Nigeria, the average annual incidence of BT between 1960 to 1963 was measured at about 4 cases/100,000 for the total population and about 9 cases/100,000 for the 0 to 14 age group (3).

Since the tumor is very rare outside Africa and New Guinea, it is unlikely that statistical tests of time-space clustering can be effectively applied except perhaps on a very coarse geographical scale. The best evidence we can expect, therefore, may be anecdotes of individual time-space clusters, none of which can be taken as firm evidence for clustering, although their detailed investigation may conceivably suggest intercase associations other than time-space closeness which can then be studied further. To date, 3 instances of time-space clustering have been reported involving BT in the United States. One of these, as mentioned above, was familial: a pair of sibs from southern California developed BT simultaneously but at unequal ages, a 17-year-old white girl and her 8-year-old brother, each with onset in July 1969 (9). The girl’s illness was most unusual since it presented as acute leukemia.

The other 2 clusters have been nonfamilial. One involved 2 boys, aged 9 and 15, both of whom became ill in August 1971 with what later was diagnosed as BT (6). Both presented with pharyngeal tumor masses. The boys lived 3 houses apart in a northern Virginia town but, remarkably enough, were not acquainted prior to onset of illness and shared no particular epidemiological features. The recent incidence of other forms of leukemia and lymphoma as well as of infectious mononucleosis in the town was reviewed and found not to be unusual. No associations were found between either of the 2 cases of BT and other local cases of leukemia or lymphoma.

The 2nd cluster involved 2 cases of BT with onsets of illness 1 month apart in white residents of a northern California town: a 9-year-old boy with onset in July 1970, and a 23-year-old man with onset in August 1970 (unpublished data). In the course of local epidemiological inquiries, a 3rd case was discovered, a 24-year-old woman from a nearby town in whom BT was diagnosed in 1972. The 2 original cases occurred in families living about 1 mile apart. No epidemiological associations were found, however, among any of the 3 cases or between them and other cancer cases. Recent local incidence of other forms of leukemia and lymphoma for the 0 to 19 age group was studied and found not to be increased and not to contain any obvious evidence of time-space clustering, with or without the cases of BT.

**Comment**

The question of time-space clustering in relation to BT needs further attention. It is not yet fully established that cases in Africa tend to come in clusters, and it is not at all clear whether significant clustering is to be expected elsewhere. In Africa, detailed evidence has been presented only for cases in the West Nile District, and findings are said to be negative in other parts of the country. Outside Africa, information is limited to 3 anecdotal accounts of clustering, 1 of them familial.

Two aspects of the existing data deserve comment. One is the fact that the space intervals at which clustering has been observed in the West Nile District (10 to 40 km) are considerably larger than what has been suggested for childhood leukemia elsewhere (4, 8) and what was observed in the 2 nonfamilial instances of BT clustering in the United States (less than 1 mile or 1 km). On first glance this discrepancy suggests 2 distinct forms of time-space clustering, coarse area-wide drift for African BT and discrete time-space aggregation for childhood leukemia and perhaps BT elsewhere. It seems likely, however, that the differing results merely reflect underlying population patterns. Since the population of the West Nile District is mostly rural and dispersed, one can infer that distances between individual homes or villages, and thus between cases, will be relatively large. In more compact, urban settings, however, shorter distances between dwelling units or cases can be expected. As a corollary, areas that contain both dense and sparse population districts might be expected to show clustering at short space intervals where population is dense and at larger intervals where population is sparse. The area surrounding Kampala may conceivably fit this description. If clustering exists, it may be detectable on a fixed-distance scale only when dense and sparse areas are examined separately. Patterns in different areas may otherwise cancel each other.

The 2nd point concerns the apparent lack of epidemiological associations other than time-space closeness among cases in individual clusters. Presumably, time-space clustering implies horizontal transmission of infectious agents. In

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*The initial cases in this cluster were originally identified through a register of BT cases maintained at the National Cancer Institute. Epidemiological inquiries concerning this cluster and the one in Virginia were conducted through the Center for Disease Control in collaboration with local and state health departments.*

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**Time-Space Clustering of Burkitt’s Tumor**
such a setting one might expect that affected persons might share particular activities or even be directly acquainted; frequency of simultaneous intrafamilial cases may be an indication of such interpersonal association. Aside from the few familial cases noted above, however, no connections are described among clustered cases. In Africa, this may just reflect difficulties in obtaining information beyond the bare facts of time and place of disease occurrence. In the American clusters, however, detailed questioning has failed to find intercase links, even when patients lived only a few doors apart (6). While the absence of links does not preclude interpersonal spread of infection, their presence would obviously support (although not prove) the idea that such time-space clustering is more than a chance affair.

References

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