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Observations on the Seasonal Pattern of Burkitt's Lymphoma in Ibadan

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Summary

Familusi JB, Adeyokunnu AA, Folami AO and Ayeni O. Observations on the Seasonal Pattern of Burkitt's Lymphoma in Ibadan. *Nigerian Journal of Paediatrics*, **1981; 8:16**. The monthly, quarterly, and half-yearly distribution of cases of Burkitt's lymphoma in Ibadan, from January 1962 to December 1974, was determined and compared with the concommitant rainfall and temperature patterns. The distribution of the tumour during the two climatic seasons of each year (namely: dry and wet seasons) was also determined. Analysis of these data have revealed no significant monthly, quarterly, half-yearly or seasonal variation in the incidence of the tumour. It is postulated that endemic malaria and Epstein-Barr virus infections are not the sole determinants of Burkitt's lymphoma oncogenesis but that a milieu of immunosuppression due to malnutrition and intercurrent infections are also important in the pathogenesis of the tumour.

Introduction

The marked variation in the geographical distribution of Burkitt's lymphoma (BL) suggests that environmental and climatic factors are important in the causation of the tumour. Because BL is most prevalent in warm and humid tropical regions, it was initially suspected that the oncogenic agent was an insect-vectored virus.[1 3] Although virological studies failed to confirm the arbovirus hypothesis, an association between BL and some other viruses, notably, Epstein-Barr virus (EBV) and reovirus type 3, was nevertheless established. EBV and reovirus type 3 were isolated from a high proportion of BL tissues, and patients with BL were also found to possess high antibody titres to the viruses.[4-6] The association was considered strongest with EBV infection.[6]

Significant relationships have also been observed between BL and chronic malaria infection. BL is only common in those regions of the world where malaria is holoendemic or hyperendemic and there are no regions where malaria is holoendemic in which BL is rare.[7-9]

While the above associations between BL on one hand, and EBV infection and endemic

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malaria on the other, strongly suggest possible aetiological relationships, they do not adequately explain all the observed phenomena. For example, EBV is world-wide in its distribution, while the geographical distribution of BL is somewhat restricted. Furthermore, it has been shown that BL may occur in patients who have no evidence of EBV infection,[10] and in the absence of endemic malaria.[11 12] Currently available evidence therefore indicates that neither the postulation of EBV infection nor of endemic malaria is adequate to explain BL oncogenesis. There is therefore, a need for the evaluation of other environmental factors that may be aetiologically related to the tumour.

Pike, William and Wright,[13] in their study of the pattern of BL in the West Nile district of Uganda, East Africa, noted that cases tended to occur in geographical clusters which shifted from year to year. This time-space clustering was interpreted to imply the involvement of a transmissible agent, probably a virus.[14] More recently, Williams, Day and Geser[15] and Williams *et al*,[16] studied the seasonal incidence and space-time distribution of BL in the same district of Uganda and observed that most cases had their onset during July to December which are the wettest months of the year. Further analysis of their data led them to postulate the existence of a tumour-provoking environmental factor which operates mainly during the rainy season, and results in tumour manifestation within a relatively short latent period of about 6 months. Specifically suspected in this regard was malaria, since vector density and malaria transmission were thought to vary seasonally with variations in rainfall. Similar findings were also interpreted by Morrow *et al*,[17] to imply that malaria was not only important in the development of BL, but also in precipitating its onset. These findings, if proven to be correct, no doubt represent significant contributions, not only to BL oncogenesis, but to the pathogenesis of tumours in general. It was therefore considered desirable to study the seasonal incidence of BL in another area of Africa in which BL is also endemic.

Materials and Methods

The records of the Ibadan Cancer Registry* as well as the admission records of all wards in the University College Hospital (UCH) for the period, January 1962 to December 1974, were examined and all cases with the coded diagnosis of BL reviewed. All cases in which the diagnosis of BL was confirmed by routine histology, or with the aid of phase contrast microscopy and/or tissue culture, were further analysed. Special note was taken of the month of onset of the illness in each patient.

The monthly distribution of cases of BL for the entire period of study was determined and compared with the concomitant rainfall and temperature patterns. For further analysis, the incidence of BL in each of the 4 quarters (namely: January to March, April to June, July to September and October to December) and in each half year, (namely: January to June, and July to December) was computed for the entire period and similarly compared with the concomitant temperature and rainfall. A special comparison was also made between the incidence of BL during the wet season (April to September) and the dry season (October to March) in each of the 13 years. The meteorological data for these comparisons were obtained from the observatory records of the Department of Geography, University of Ibadan.

Results

During the 13 years under consideration, a total of 772 patients with confirmed diagnosis of Burkitt's lymphoma were registered in the Ibadan Cancer Registry. The time of onset of illness could be determined in 594 of these, but in the remaining 178, this was not possible either because the patients were managed in medical centres other than UCH, and thus the case

*The Cancer Registry was established in 1960 with the assistance of the British Empire Cancer Campaign Fund.

records were not available to us, or because this information was not recorded in the case-notes by the attending physicians.

The 594 patients consisted of 372 males and 222 females, giving a M:F ratio of approximately 3:2. Five hundred and fifty-four patients (91%) were children under the age of 16 and a majority of these were aged, 4–12 years, with a peak around 7 years. Twenty-eight patients were aged twenty years and above, and these were mostly pregnant women, or women with a recent history of child birth.

Table I shows the number of BL cases by year and month of onset of illness. For each year from 1962 to 1974 and as indicated by the chi squared values in the last column of the table, there was no monthly variation ($P > 0.05$) in the number of cases.

The quarterly, half-yearly, and seasonal distribution of cases are summarized in Tables II, III and IV respectively. Of the thirteen years under consideration, only in 1970 was there a significant ($P < 0.05$) quarterly variation in the occurrence of cases. Significant half-yearly variation ($P < 0.05$) also occurred during 1969 and 1970, although the pattern of variations was not consistent for both years. With regards to the distribution of cases in relation to the 2 major climatic seasons, significant seasonal variation ($P < 0.05$) was evident only during 1973.

Table V presents the Pearson's coefficients of correlation between the monthly number of cases, and (*a*) mean monthly temperature, and (*b*) total monthly rainfall for the period, January 1964 to December 1973. For temperature, the correlation was significant ($P < 0.05$) in 1969 and in 1970, but while the correlation was negative in 1969, it was positive in 1970. None of the coefficients for rainfall was significant.

TABLE I

Monthly Distribution of 594 Cases of Burkitt's Lymphoma in Ibadan

Year	*Month*												*Total*	X^2
	J	*F*	*M*	*A*	*M*	*J*	*J*	*A*	*S*	*O*	*N*	*D*		
1962	3	5	3	5	2	4	1	5	3	0	4	1	36	10.67
1963	1	3	2	4	1	2	5	4	2	3	5	4	36	7.33
1964	4	4	4	6	3	3	3	5	11	1	4	3	51	15.59
1965	1	3	6	2	2	2	2	5	5	3	5	6	42	10.00
1966	5	4	4	3	3	4	2	3	3	2	0	6	39	8.08
1967	6	2	7	5	3	1	3	7	4	5	4	6	53	9.26
1968	7	3	9	4	4	4	5	2	7	2	3	4	54	11.33
1969	2	2	2	2	4	3	5	7	5	7	5	1	45	12.33
*1970	3	7	5	8	3	8	1	1	2	4	4	3	49	16.39
1971	6	7	7	3	1	3	7	5	4	4	4	2	54	10.00
1972	3	2	4	8	6	5	1	5	4	3	9	3	53	13.79
1973	5	1	1	4	6	8	3	7	5	3	3	4	50	12.40
1974	4	4	3	1	5	3	3	4	2	0	0	3	32	10.75

*$P < 0.05$

TABLE II

Quarterly Distribution of 694 Cases of Burkitt's Lymphoma in Ibadan

Year	No. of Cases				Percentage Distribution				X^2
	Q_1	Q_2	Q_3	Q_4	Q_1	Q_2	Q_3	Q_4	
1962	11	11	9	5	30.6	30.6	25.0	13.8	2.67
1963	6	7	11	12	16.7	19.4	30.6	33.3	2.89
1964	12	12	19	8	23.5	23.5	37.3	15.7	4.92
1965	10	6	12	14	23.8	14.3	28.6	33.3	3.33
1966	13	10	8	8	33.3	25.6	20.5	20.5	1.72
1967	15	9	14	15	28.3	17.0	26.4	28.3	1.87
1968	19	12	14	9	35.2	22.2	25.9	16.7	3.93
1969	6	9	17	13	13.3	20.0	37.8	28.9	6.11
1970	15	19	4	11	30.6	38.8	8.2	22.4	10.02*
1971	20	7	16	11	37.0	13.0	29.6	20.4	7.19
1972	9	19	10	15	17.0	35.8	18.9	28.3	4.89
1973	7	18	15	10	14.0	36.0	30.0	20.0	5.84
1974	11	9	9	3	34.4	28.1	20.1	9.4	4.50
Total	154	148	158	134	25.9	24.9	26.6	22.6	2.23

*P < 0.05 Q_1 — January-March Q_2 — April-June Q_3 — July-September Q_4 — October-December

TABLE III

Half-Yearly Distribution of 594 Cases of Burkitt's Lymphoma in Ibadan

Year	No. of Cases		Percentage Distribution		X^2
	S1	S2	S1	S2	
1962	22	14	61.1	38.9	1.78
1963	13	23	36.1	63.9	2.78
1964	24	27	47.1	52.9	0.18
1965	16	26	38.1	61.9	2.38
1966	23	16	59.0	41.0	1.26
1967	24	29	45.3	54.7	0.47
1968	31	23	57.4	42.6	1.1
1969	15	30	33.3	66.7	5.00*
1970	34	15	69.4	30.6	7.57*
1971	27	27	50.0	50.0	0.00
1972	28	25	52.8	47.2	0.17
1973	25	25	50.0	50.0	0.00
1974	20	12	62.5	37.5	2.00
Total	302	292	50.8	49.2	0.17

*P < 0.05
S1 = January to June S2 = July to December

The above results may be artefacts if there had been considerable variations in the total admissions pattern in the hospital. Therefore similar statistical analysis was performed on both the inpatients and the outpatients admission figures. Relevant data were available for the years, 1965 to 1973, and analysis of these revealed significant quarterly, half-yearly, as well as seasonal variations in the admission figures. The pattern of variation was however, not consistent in that the series was equally likely to show a pattern for one year and a directly opposite pattern in the following year. To remove these and other complications introduced by variations in the total hospital admissions, rates of diagnosis of BL per (*a*) 10,000 inpatients and (*b*) 10,000 outpatients were determined and computed quarterly, half-yearly, and seasonally. When these quarterly, half-yearly, and seasonal rates were ranked within each year and statistically compared by applying

TABLE IV

Seasonal Distribution of 594 Cases of Burkitt's Lymphoma in Ibadan

Year	No. of Cases		Percentage Distribution		X^2
	Dry Season (Oct.-March)	Wet Season (April-Sept.)	Dry Season (Oct.-March)	Wet Season (April-Sept.)	
1962	16	20	44.4	55.6	0.44
1963	18	18	50.0	50.0	0.00
1964	20	31	39.2	60.8	2.37
1965	24	18	57.1	42.9	1.17
1966	21	18	53.8	46.2	0.23
1967	30	23	56.6	43.6	0.92
1968	28	26	51.9	48.1	0.07
1069	19	26	42.2	57.8	1.09
1970	26	23	53.1	46.9	0.18
1971	31	23	57.4	42.6	1.19
1972	24	29	45.3	54.7	0.47
1973	17	33	34.0	66.0	5.12*
1974	14	18	43.8	56.3	0.50
Total	288	306	48.5	51.1	0.55

*$P < 0.05$

TABLE V

Burkitt's Lymphoma in Ibadan: Pearson's Coefficients of correlation between monthly number of cases and (a) mean monthly temperature (b) total monthly rainfall.

Year	(a)	(b)
1964	−0.05	0.05
1965	−0.01	−0.36
1966	0.04	−0.18
1967	−0.03	−0.37
1968	0.03	−0.24
1969	−0.68*	0.37
1970	0.64*	0.10
1971	0.04	−0.09
1972	0.07	0.03
1973	−0.52	0.50

*$P < 0.05$

TABLE VI

Kendall's Coefficient of Concordance in Respect of Quarterly, Half-Yearly, and Seasonal Diagnostic Rates of BL per 10,000 Patients.

Variation	Outpatients		Inpatients	
	Kendall's Coefficient of concordance	Statistical significance	Kendall's Coefficient of concordance	Statistical significance
Quarterly	0.001	P > 0.5	0.010	P > 0.5
Half-Yearly	0.012	P > 0.5	0.023	P > 0.5
Seasonal	0.082	P > 0.5	0.023	P > 0.5

Kendall's coefficient of concordance, there was no consistent quarterly, half-yearly, or seasonal variation in the magnitude of the diagnosis rates over the nine-year period (Table VI), thereby confirming the results in Tables I to V.

Discussion

The present study has not confirmed the seasonal variation in the incidence of BL observed in the West Nile District of Uganda by Williams *et al.*[15] This is rather unexpected because rainfall which was the major climatic variable in the study by Williams and his co-workers show greater seasonal variations in Ibadan and environs than in the West Nile district of Uganda. The rainfall pattern recorded by Williams *et al*[15] as well as other published meteorological data[18] show that the West Nile district enjoys a remarkably uniform distribution of rainfall. The dry season lasts for only a month or two, and even during this period, there are usually some light showers. In contrast, Ibadan and its environs have a more truly tropical climate characterized by a long rainy season of about six months, followed by a dry period of about the same period. If the rainfall pattern is responsible for the observed seasonal variation in the incidence of BL in the West Nile district, then Ibadan, by virtue of its rainfall pattern, should have an even more pronounced seasonal variation in the incidence of the disease.

Morrow *et al*,[17] working in the Mengo districts of Uganda also found a seasonal variation in the incidence of BL, but unlike in the nearby West Nile district, a majority of their cases occurred during the first half of the year. Furthermore, their study did not reveal any correlation between the prevailing rainfall pattern and the onset of BL cases. These findings, taken in conjunction with our own therefore suggest that the seasonal variation in the onset of cases of BL observed in the West Nile district of Uganda does not necessarily hold good in every area of BL endemicity.

The currently favoured theory that EBV infection and endemic malaria are the two principal factors in BL oncogenesis also requires reevaluation. It has already been emphasized that chronic malaria is unlikely to play any significant role in cases of BL occurring in malaria-free areas of Europe and North America. Similarly, EBV infection cannot be an invariable factor in BL oncogenesis since it is known that BL can occur in the absence of EBV infection. For instance, a recent study[10] revealed that while high EBV antibody titres were present in virtually all African patients with BL, as many as one third of American patients had no detectable EBV antibodies. These workers further reported that the titres of EBV antibodies in American patients with BL did not differ significantly from those found in an age, sex, and race–matched control group. It seems therefore that in the American situation at least, neither chronic malaria nor EBV infection is a constant accompaniment of BL. Unless BL in the American is aetiologically different from the African disease, acceptable explanations are necessary for these conflicting observations.

It is now widely recognized that disturbances of the host's immune system play significant roles in the pathogenesis of most neoplasms. According to current concepts,[19 20] a breakdown in the immunological surveillance of the host permits the proliferation of an abnormal clone of cells with a selective advantage over other cells. In the case of BL oncogenesis, it has been further suggested that persistent stimulation of the lymphoreticular system by chronic and heavy malaria infection creates the background of immunological disturbance which pre-conditions the lymphoid tissues to oncogenic transformation by EBV,[14 21] Such a postulate no doubt accords with the observed preponderance of BL in areas of malaria endemicity,[2 21] the frequent isolation of EBV from BL tissues,[4] the presence of EBV antibodies in a high percentage of BL patients,[6 22] and the demonstrated lymphotrophic and oncogenic potential of EBV in experimental animals including primates.[23-25]

Nevertheless, it seems improbable that malaria and EBV infections can be directly involved in cases of BL occurring in non-malarious areas and without any evidence of EBV infection. In such cases therefore, the required milieu of immunosuppression is likely to be due to non-malarial factors, while other agents besides EBV provoke the subsequent oncogenic transformation of the

lymphoid tissues. Even in malarious areas, it is also likely that the milleu of immunological derangement which predisposes to BL is not due to malaria infection alone, but to other factors as well. This is because malaria is but one of several infections that are prevalent in these areas, which are predominantly in the economically-backward regions of the world. The immune systems of children living in such areas are constantly challenged by several endemic infections, and it may therefore be difficult to single out any one infection as being predominantly responsible for deranging the immune system. The prevailing childhood malnutrition in such areas of the world may also be contributory by interacting with multiple infections to compromise the immune system further. All the BL patients studied by Clifford *et al*[26] as well as 99 per cent of those reported by Aderele and Antia[27] were poorly nourished children from low socioeconomic backgrounds. In contrast, BL is rare in well nourished children of higher socio-economic background sharing the same climatic environment. It seems evident therefore, that the pathogenesis of BL is very likely multifactorial. This view is similar to previous suggestions by Williams[28] and by Aderele and Antia[27] and is in our opinion more consistent with all the observed facts about BL than are the more widely held views which incriminate mainly malaria and EBV infections in the pathogenesis of the disease.

It remains unexplained however, how the summation of the multiple factors involved in BL oncogenesis will result in seasonal variation in the incidence of the disease in some geographic areas, but not in others. Detailed analysis of the seasonal variation of all the potentially oncogenic factors in various areas of BL endemicity may produce useful insight into this question, but such an undertaking is in our opinion formidable. Instead, efforts should be directed towards improving the nutritional status of the community as well as towards eradicating prevalent infections (including malaria) because these will in our opinion, result in significant reduction in the incidence of BL in those tropical areas where the tumour is currently endemic. If that proves to be the case, then BL will join the list of the so-called tropical diseases which are caused predominantly by socio-economic factors.

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