ORIGINAL ARTICLE

Seasonality of Burkitt's lymphoma in Uganda

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ABSTRACT

Background/Aims: Burkitt's lymphoma is the most common childhood oral maxillofacial tumor in Africa and some studies have reported seasonal variation. **Materials and Methods:** All Burkitt's cases diagnosed from 1969 to 2006, from all over Uganda, at the Makerere University's Department of Pathology, were analyzed, to determine seasonal variation. This was done by evaluation of monthly and rainy versus dry season prevalence. **Statistical analysis:** The Wilcoxon test was used in both cases, to assess the statistical significance of differences in the diagnostic rates of Burkitt's lymphoma, in comparison to nonspecific chronic inflammation, using the total as the denominator. Yearly variation in prevalence was examined by a Chi-square test for linear trend. Mann-Whitney tests were done to compare the climatic regions. Multivariate analysis of variance (MANOVA) was used to test for differences when gender, seasons and climatic regions were factored in. **Results:** Although monthly frequencies varied considerably over the period, none of the differences were statistically significant (Pearson's 15.199, degrees of freedom df = 11, P = 0.174). Likewise, there was no statistically significant difference in the total number of Burkitt's and nonspecific chronic inflammation biopsies handled at the Department during the rainy and dry seasons. **Conclusion:** Although the 38-year period gave us sufficient numbers to use the Edward's method for seasonality, it also meant that a lot of seasonal changes that occurred during the period were not taken into consideration. We hence feel that a review of this data with weather experts, so as to group the biopsies into accurate rainfall and dry patterns, would yield a more authoritative publication.

Key words: Burkitt's lymphoma, lymphomas, Non-Hodgkin's disease, seasonal variation

INTRODUCTION

Some previous reports have shown significant evidence of seasonal variation in the onset of Burkitt's lymphoma, diagnosed based on the time of the first symptom, both within and outside Uganda.[1-3] The finding of seasonal variation is consistent with an infectious etiology. Hodgkin's disease and Burkitt's lymphoma have been associated with Epstein-Barr virus (EBV).[4,5] However, other studies[6-8] have found no evidence of seasonal variation of Hodgkin's disease and Burkitt's lymphoma. In addition, other previous studies[9-11] have reported Burkitt's lymphoma endemicity to coincide with rainfall, low altitude, as well as malaria endemicity. It has been postulated that an increase in the incidence of Burkitt's lymphoma seen during the rainy seasons may be due to increased mosquitoes that breed during the season, yet they are vectors for EBV. Furthermore, the rainy seasons also come with an increase in malaria infections, which is suspected to compromise the immunity, leading to increased susceptibility to Burkitt's lymphoma.[11,12] The aim of this study is to assess seasonal variations in Burkitt's lymphoma compared to nonspecific chronic inflammation histologically diagnosed between 1969 and 2006, in the Ugandan population.

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MATERIALS AND METHODS

Study design

This was a retrospective study involving a review of patients' histological specimen records from 1969 to 2006.

Study area and population

The patients' records were retrieved from the archives of the Department of Pathology, College of Health Sciences, Makerere University. The Department is within the Mulago National Referral Hospital Complex, Uganda. Up until 2006, the Department was the only place in Uganda where histological investigations were available and all specimens of suspected lymphomas were sent for diagnosis. The study population comprised of all patients whose biopsies had a histological confirmation of Burkitt's lymphoma, while the comparison group was of those diagnosed with nonspecific chronic inflammation.

Study variables

The information recorded included the histological diagnosis (Burkitt's lymphoma or nonspecific chronic inflammation), the age and sex of the patient, district of residence in Uganda at onset of the clinical symptoms and the month of the year when the patient first went to a health facility. In a bid to establish a relationship between prevalence and seasonal patterns of the different regions of Uganda, we grouped the data using the meteorologically defined rainfall seasons in Uganda, as previously described.[13] The regions in Uganda were categorized as Lake Basin and Central (included areas A1, A2, B and D) = 1, Western and Southwestern (included areas C and M) = 2, Northwestern and North Central (included areas L, K, I and J) = 3, Northeastern (included areas H and G) = 4 and Eastern and East Central (included areas E and F) = 5 [Figure 1].

Ethical considerations

Permission to carry out the study was obtained from the Mulago National Referral Hospital's Ethical and Research Committee.

Data analysis

The data were entered into a computer and analyzed using the Statistical Package for Social Sciences Inc. (Version 15 for Windows, Chicago, Illinois, USA). Frequency distribution was used to summarize the data. Seasonal variability was determined by evaluation of monthly prevalence, rainy versus dry seasons. The Wilcoxon test was used in both the cases to assess the statistical significance of differences in the diagnostic rates of Burkitt's lymphoma and nonspecific chronic inflammation, using the total as the denominator. Yearly variation in prevalence was examined by the Chi-square test for linear trend. The chi square test was done to compare the mean age, while the Mann-Whitney tests were done to compare the climatic regions. The MANOVA was used to test for differences, if gender, seasons and climatic regions were factored in. The level of significance was set at 5%.

RESULTS

The study sample had 2497 medical records of cases histologically diagnosed as Burkitt's lymphoma and a comparison group of 2096 cases of nonspecific chronic inflammation during the period 1969-2006. About 59.7% (1490) of the Burkitt's lymphoma and 57.7% ($n = 1209$) of the nonspecific chronic inflammation cases were male. This finding did not have a statistically significant difference ($\chi^2 = 1.41$, df = 1, $P > 0.05$). The overall age range of the patients was 1 to 94 (mean 15.4 ± 15.7 years, mode 6 and median 9) years. The Burkitt's lymphoma cases were significantly younger when compared with the nonspecific chronic inflammatory counterparts: Range 1 to 80 years (mean 8.1 ± 6.3) versus 1 to 94 years (mean 24.5 ± 18.8 years, mode 6 and median 7, $P > 0.05$).

On the basis of the month of biopsy/first time of reporting to hospital, generally the prevalence of both Burkitt's lymphoma and nonspecific chronic inflammatory lesions tended to be lower during the month of April and higher during September [Figure 2]. However, there was no statistically

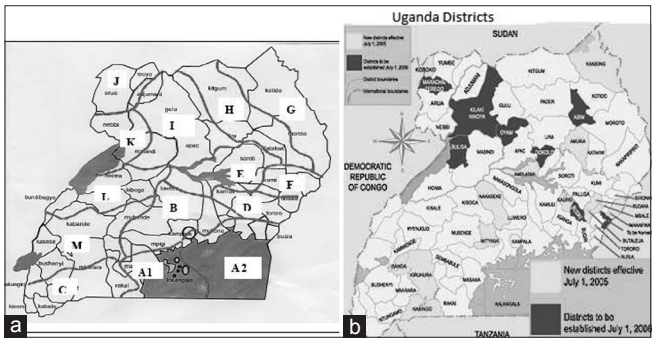

Figure 1: The maps of Uganda showing different regional rainfall patterns (a) and districts as of 2006 (b)

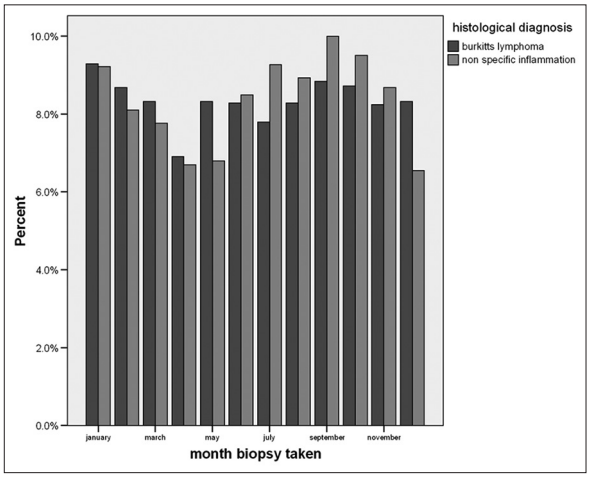

Figure 2: The frequency distribution of cases based on the histological diagnosis of Burkitt's lymphoma (n = 2497), nonspecific chronic inflammation (n = 2096) and month of onset of symptoms

significant difference between the monthly diagnostic rates of cases with Burkitt's lymphoma and those with nonspecific chronic inflammation (χ^2 = 15.2, df = 11, $P > 0.05$). When the material was analyzed based on the rainfall pattern, there was no statistically significant difference in the cases with Burkitt's or nonspecific chronic inflammation, between the rainy and dry seasons. About 47.9% (n = 1195) of the Burkitt's lymphoma cases and 49.4% (n = 1036) of the nonspecific chronic inflammation cases were diagnosed during the rainy season (Wilcoxon W = 1437600, Z = 0.00, P = 1.000, Wilcoxon W = 877332, Z = 0.000, P = 1.000, respectively).

A Chi-square test for linear trend was performed to assess whether the yearly prevalence rates had significantly changed over the course of the study period. There was a significant linear increase in the frequency of both Burkitt's lymphoma and nonspecific chronic inflammation specimens over time (χ^2 = 4303.2, $P < 0.05$).

The districts of residence where grouped into the climatic regions of Uganda [Figure 1], the Lake Basin and Central region had the highest number of cases for both Burkitt's lymphoma and nonspecific chronic inflammation. These were followed by the Eastern and Central region and then the Northwest and North Central Region [Figure 3]. This difference was statistically significant (χ^2 = 3523.2, df = 4, $P < 0.05$). Table 1 shows the significant differences resulting from the Mann-Whitney tests, with histological diagnosis as the test variable and climatic regions as the grouping variable. However, for all the regions, there was no statistically significant difference between the rates of diagnosis for Burkitt's lymphoma and nonspecific chronic inflammation (Z = 0.68, P = 0.49).

A MANOVA, to assess any significant differences between the Burkitt's lymphoma and nonspecific chronic inflammatory group, on a linear combination of seasons of the country and the climatic regions, showed no statistically significant difference (Wilk's λ =0.999, F(4144) =2.59, $P > 0.05$, $\acute{\eta}$ =0.001). Similarly, when MANOVA was used to assess any significant difference between the Burkitt's lymphoma and nonspecific chronic inflammatory group on a linear combination of seasons of the country, the climatic regions and gender, it showed no significant difference (Wilk's λ =0.999, F (4127) =1.85, $P > 0.14$, $\acute{\eta}$ =0.005).

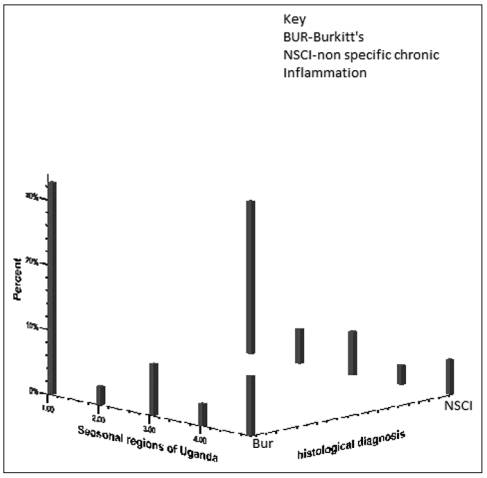

Figure 3: The frequency distribution of patients based on the histological diagnosis of Burkitt's lymphoma (n = 2597) and nonspecific chronic inflammation (n = 2096)

DISCUSSION

In the present study, there was no significant seasonal variation observed in the occurrence of Burkitt's lymphoma or nonspecific chronic inflammation over the 38-year (1969-2006) period. This finding was in agreement with Williams *et al.*[14] and Oguonu *et al.*,[15] who reported a higher but not statistically significant difference in prevalence of Burkitt's lymphoma in the dry season as compared to the wet season, in Uganda and Nigeria, respectively. However, contrary to our finding, Hesseling *et al.*, Van Den Bosch and Lloyd[12,16] had previously observed a significantly higher occurrence of Burkitt's lymphoma in the wet season as compared to the dry one in South Africa and Malawi, respectively.

Similar to nonspecific chronic inflammation, Burkitt's lymphoma did not appear to affect one particular climatic region of the country and monthly and seasonal variations in prevalence were random, hence no distinct patterns could be established (Figure 4 shows the monthly distribution per climatic region). Incidentally there was a suggestion of increased prevalence of nonspecific chronic inflammation during the rainy season, which was statistically significant (Pearson's χ^2 =5.27, df = 1, P = 0.02). The explanation for the increased prevalence of nonspecific chronic inflammation in the rainy season was not obvious. However, it is worth noting that rainfall affects the road network, making access to healthcare facilities more difficult. Stephenson *et al.*,[17] reported rainfall as one of the factors affecting the chances of giving birth in hospitals in Kenya, but no significant influence was reported in other countries. If the road conditions were a factor, it would be expected that there would be a decline of patients reporting to the hospital

Table 1: The significant differences in the number of biopsies from the different climatic regions of Uganda

Climatic Regions	Significance	*Z*-value
Lake Basin and central region (1) versus Western and South Western Region (2)	0.004	2.87
Western and South Western Region (2) versus North West and North Central Region (3)	0.001	8.165
Western and South Western Region (2) versus North East Region (4)	0.001	4.34
Western and South Western Region (2) versus East and Central Region (5)	0.001	5.77
North West and North Central Region (3) versus East and Central Region (5)	0.001	7.99

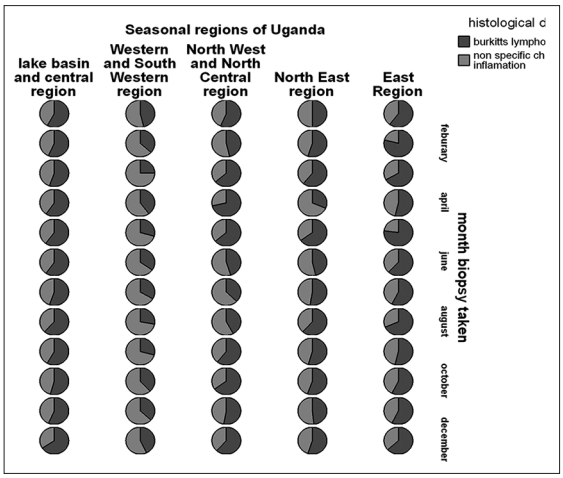

Figure 4: Shows the monthly distribution of cases diagnosed as Burkkit's and nonspecific chronic inflammation, as per the different climatic regions of Uganda

during the rainy season. This would affect the number of biopsies taken for either chronic nonspecific inflammation or Burkitt's lymphoma equally. However, the fact that this pattern was not noted among Burkitt's lymphoma cases, might suggest an influence of chance. On the other hand, given the clinical course of Burkitt's lymphoma, it might as well be said that no matter what the status of the roads, the patients' relatives would do whatever it took to get them to hospital. It is worth noting that the period covered 38 years. During this period, the country has seen changes in rainfall patterns due to the El Nino effect, implying that the months that we grouped in the wet and dry seasons might actually have had a different seasonal pattern during the constituent calendar years.[18]

No evidence for significant variation in rates of diagnosis could be found between the climatic regions of the country. The significant differences between the climatic regions in terms of contribution to the total biopsy results, as shown in Table 1, could well be explained by the population distribution of the country, with the Lake Basin and Central Region being the most highly populated.[19] Secondly, the region is closest to the place of histological diagnosis, the Department of Pathology, within the Mulago Hospital Complex, where most of the complicated medical cases in the region were referred. This implied that all biopsy specimens taken to Mulago Hospital had an easy access to the Histological Laboratory, as compared to those from up-country health facilities. A similar trend was previously seen in the Gulu District, Uganda, where areas closest to St. Mary's Lacor Hospital contributed the bulk of the specimens taken at the hospital.[20] The present study did not show any evidence of significant differences between the histological groups on a linear combination of seasons and climatic regions, in Uganda. Boerma *et al.*[21] reported differences in age distribution between males and females, with the males having a bi-modal peak. This report prompted us to test for any gender difference in seasonal patterns and climatic regions. In our study there were no significant differences noted when gender was included in the analysis. Therefore, gender did not play a role in the seasonal variation of both conditions.

The significant increase in the frequency of both Burkitt's lymphoma and nonspecific chronic inflammation specimens over the 38-year period is not an unexpected outcome given the fact that Uganda has registered an increase in population over this period,[22] which may partly explain the increase in the prevalence of both lesions. A similar trend has previously been reported in Uganda for malaria, before intervention with insecticide-treated mosquito nets.[23] Therefore, the increase in the number of biopsies over the period is likely to be in consort with the population dynamics and increased awareness.

Although the 38-year period gave us sufficient numbers to use the Edward's method[24] for seasonality, it is probable that a number of seasonal changes that occurred during the period may not have been taken into consideration, thus influencing our findings. We hence feel that a review of this data with weather experts, so as to group the biopsies into accurate rainfall and dry patterns, will yield a more authoritative publication.

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