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Epidemiology of Childhood Leukaemias and Lymphomas with Special Reference to Ibadan

CKO WILLIAMS*

Summary

Williams CKO. Epidemiology of Childhood Leukaemias and Lymphomas, with Special Reference to Ibadan. *Nigerian Journal of Paediatrics*, **1985; 12:1.** The peak incidence of acute lymphoblastic leukaemia (ALL) in the first and second quinquennia characteristically observed in economically advanced societies of the world is lacking in Ibadan, but an increased occurrence of chloroma-associated variant of acute myelogenous leukaemia (AML) is evident. Burkitt's lymphoma (BL) which is only rarely encountered among caucasians of Western Europe and North America is the most common childhood malignancy in Ibadan, with a relative frequency of slightly over 50% of all paediatric tumours. Evidence is presented to show that the reduced incidence of ALL in the first two quinquennia and the increased incidence of chloroma-associated AML in Ibadan, probably represent a biological phenomenon resulting from thymo-lymphatic deficiency due to malnutrition and infection in early life. Similarly, the high relative frequency of BL is attributable to high prevalence of acquired immunodeficiency in children of the area.

Introduction

THE role of environmental factors in the aetiology of neoplastic diseases is being increasingly realized. Given the marked disparity in the socio-economic environments of people in the developing and developed countries, it is reasonable to suspect that the marked differences that exist in the patterns of childhood leukaemias and lymphomas in these areas of the world are due to environmental factors. Elucidation of the roles of such factors may help in the control of these diseases in the future.

University College Hospital, Ibadan.

Department of Haematology
*Senior Lecturer

Relative Incidence

The relative frequencies of childhood malignancies as observed in two earlier studies from Ibadan by Edington and McLean[1] and Williams[2] are shown in Table I. The former authors based their report on cases from various parts of the city of Ibadan as observed between 1960 and 1963, while the latter author's report included

all childhood malignancies recorded at the Ibadan Cancer Registry between 1960 and 1972. Burkitt's lymphoma (BL) constituted slightly more than half of all the malignancies seen in the two studies. The Ibadan city data contained almost twice as high a percentage of leukaemia cases as in the series based on data derived from all sources, Ibadan city inclusive. Of interest is the relative frequency of retinoblastoma cases which constituted 7.4% in the report by Williams[2]. Furthermore, Table I compares Ibadan figures with the relative frequencies of the malignancies in black and white United States of America (US) children[3] as well as with those of the Manchester (England) Children's Tumour Registry[4]. In these 3 latter populations, leukaemias constituted roughly, a quarter to a third of all chidhood malignancies, while Burkitt's lymphoma was extremely infrequent in the US populations and absent in the Manchester data.

Table II shows the rank order of the 6 commonest childhood malignancies in Ibadan area of Nigeria, the US and Manchester area of England. The most striking feature here is the inverse relationship in the relative frequencies of BL and leukaemia in Nigeria compared with the US and England. The other striking feature is what appears to be an inverse relationship between the relative frequencies of retinoblastoma and brain tumours in Nigeria as compared to the US and England. All other common childhood tumours like neuroblastoma, Wilm's tumour, the soft tissue sarcomas and the Non-Burkitt's lymphomas occupy similar positions in their order of relative frequency in the four populations studied. These observations indicate that some unknown environmental factors may be at play in respect of the haemopoietic and lymphoreticular neoplasia, whereas diseases like Wilm's tumour, neuroblastoma and soft tissue sarcomas are not subject to such environmental factors.

Socio-economic Status and the Incidence of Leukaemia/Lymphoma

There are strong indications that socio-economic rather than genetic factors are responsible for the marked difference in the relative incidences of leukaemia/lymphoma observed in Nigeria and in developed countries of the world. An important indication in this regard is the observation of changes in the leukaemia/lymphoma ratio within the same ethnic group over a long period of observation. Such observation has been made over a period of 8 years among young Arabs living in the Gaza strip[5]. The period of study was marked by rapid economic development, with about 300% increase in the *per capita* Gross National Product and associated increases in available housing and household appliances. During the study period, there was a statistically significant progressive alteration in the leukaemia/lymphoma ratio among the previously underprivileged Arab population, but not among Jews seen in the same area[5].

Unconfirmed reports have claimed a consistently progressive drop in the incidence of BL in various African centres, including Nairobi, Accra and Ibadan (CLM Olweny, FK Nkrumah and AA Abioye: personal communications). It has recently been demonstrated that the annual accrual rate of acute lymphoblastic leukaemia (ALL) seen in Ibadan between 1978 and 1982 has increased almost 3-fold compared to that of the period 1958–1968 and much of the change occurred in the first 3 quinquennia . The annual accrual rates of acute myelogenous leukaemia (AML) did not, however, change remarkably over the same period of observation[6]. Thus, the pattern of incidence of ALL and BL appears to be undergoing a gradual but definite change in the same direction as that of the earlier observations from the Gaza strip cited earlier. As in that study, it is conceivable that these changes are occurring consequent upon recent favourable socio-economic changes in parts of Nigeria.

TABLE I

Percentage Distribution of the Relative Incidences of 10 Childhood Malignancies in Ibadan, in the US and in Manchester (England)

	*Ibadan** (*Edington & McLean*[1], 1960–1963) *n*=101	*Ibadan*** (*Williams*[2], 1960–1972) *n*=1325	*US Blacks* (*Young & Miller*,[3] 1969–1971) *n*=1925	*US Whites* (*Young & Miller*[3], 1969–1971) *n*=1925	*Manchester (England)* (*Birch et al*,[4] 1954–1977 *n*=2442
Burkitt's lymphoma	50.4	51.5	0.009	0.004	0
Retinoblastoma	NA	7.4	3.1	2.7	3.0
Sarcoma of connective tissue	3.0	6.3	4.0	6.8	5.9
Wilm's tumour	5.0	5.6	8.0	6.1	5.1
Leukaemia	8.9	4.5	24.8	33.8	33.1
Neuroblastoma	NA	2.6	6.2	6.4	6.4
Brain and other CNS tumours	4.9	2.2	24.3	19.2	15.8
Non-Hodgkin's lymphoma	2.0	2.7	7.1	5.6	4.5
Hodgkin's lymphoma	2.0	4.0	6.2	4.6	3.6
Others	23.8	13.2	16.3	14.8	22.6

US = United States of America
* Ibadan City only
** All cases in Ibadan Cancer Registry
n = No of cases studied
NA = Not available

TABLE II

Rank Order of the Six Commonest Childhood Malignancies seen in Ibadan, the US and Manchester (England)

Rank	*Ibadan*	*US Blacks*	*US Whites*	*Manchester (England)*
1.	Burkitt's lymphoma	Leukaemia	Leukaemia	Leukaemia
2.	Retinoblastoma	Brain and other CNS tumours	Brain and other CNS tumours	Brain and other CNS tumours
3.	Non-Burkitt's lymphoma	Non-Burkitt's lymphoma	Non-Burkitt's lymphoma	Non-Burkitt's lymphoma
4.	Connective tissue sarcoma	Wilm's tumour	Connective tissue sarcoma	Neuroblastoma
5.	Wilm's tumour	Neuroblastoma	Neuroblastoma	Connective tissue sarcoma
6.	Leukaemia	Connective tissue sarcoma	Wilm's tumour	Wilm's tumour

US = United States of America

Influence of Socio-economic Status on Leukaemia/Lymphoma Subtypes

(*i*) *Acute leukaemia*

With the advent of monoclonal antibodies, it has become possible to subclassify ALL into 4 subtypes: common ALL (c-ALL), thymic-ALL (T-ALL), null-ALL and Burkitt-cell ALL (B-ALL)[7]. These subtypes of ALL have different biological behaviours: c-ALL is the least aggressive and most highly responsive to chemotherapy of the four subtypes. It is curable in about 50% of its victims. T-ALL and B-ALL are much more aggressive than c-ALL while null-ALL is intermediate in its clinical course. C-ALL of childhood has a characteristic peak in the 2–5 year age group, while T-ALL occurs mainly in late childhood and does not show the early childhood peak[8]. Childhood ALL with its characteristic 2–5-year age-group peak, c-ALL immunological characteristics and favourable prognosis, is typically a disease of the affluent societies[5]. Reports from different parts of Africa suggest that this type of ALL is rare in indigenous African populations in whom leukaemia epidemiology has been studied[8-12]. Apart from the age-distribution of childhood ALL as seen in Ibadan and other centres of Black Africa, the clinical and laboratory findings of this disease are highly suggestive of a deficit of c-ALL and a preponderance of T-ALL in Black Africa (unpublished observation). Furthermore, Williams and his colleagues[13] have estimated that although childhood acute myelogenous leukaemia (AML) has a similar incidence rate in Ibadan as compared to Europe and the USA, the incidence of childhood ALL in Ibadan was only one-third of that of European and white US children. The latter observation is probably attributable to a deficit of c-ALL.

In Ibadan, the socio-economic background of children with ALL is significantly higher than that of those with AML especially when the latter disease is a variant that is associated with chloroma formation[6]. Furthermore, the younger the child with ALL, the more likely he is to have come from a home of a higher socio-economic status[6]. There is, however, no information on the relationship between the immunologic variant of ALL and socio-economic status, and it is not clear whether these observations among leukaemia children in Ibadan represent another early trend in the transformation of the leukaemia pattern in the area towards that of more affluent societies.

(*ii*) *Burkitt's lymphoma*

Although the geographical spread of this disease coincides with the region of the world with hyperendemic malaria[14 15], it is quite clear that individuals living in this "endemic" zone are differentially affected and this is likely to be a result of several socio-economic factors that were recently outlined[16]. While the report suggests that "endemic" BL develops on a background of socio-economic and educational deprivation, it does not explain the occurrence of BL in sporadic fashion in "non-endemic" areas of Europe and America. It now appears that BL is a "world-wide" disease. It has, for example, recently been shown to be the most common Non-Hodgkin's lymphoma among French children[17], even though it occurs there only at a low incidence.

(*iii*) *Non-Burkitt's lymphoma (NBL)*

This group of lymphoproliferative disorders include (*a*) Hodgkin's and (*b*) Non-Hodgkin's lymphoma. As shown in Table II, the Non-Burkitt's lymphomas occupy similar position in the rank order of frequency of childhood neoplasia in Ibadan, US, and Manchester, thus, suggesting that the incidence of NBL is not subject to remarkable environmental factors. This, however, is probably not so, as epidemiological evidence is available in support of environmental influence, at least, in the aetiology of Hodgkin's lymphoma.

(*a*) *Hodgkin's lymphoma (HL)*

Four epidemiological variants of Hodgkin's disease are recognizable[15 18 19]. A variant that occurs frequently in childhood in parts of Africa is usually associated with those histological types

that portend poor prognosis. It is found in developing countries where socio-economic standards are suboptimal. It is interesting to note that the incidence of childhood HL in a given community varies inversely with the community's Gross National Product (GNP)[20]. In Uganda, proportionately more children are afflicted with Hodgkin's lymphoma during the first 5 years of life than in Europe or North America[21 22]. In a recent series of 21 HL patients reported from Ibadan, 9 (42.7) were children, none of whom was below the age of 5 years[23]. Thus, while HL in childhood is not uncommon, the disease is rare below the age of 5 years in Ibadan.

(*b*) *Non-Burkitt's (Non-Hodgkin's lymphoma (NBL/NHL)*

This is a heterogeneous group of lymphoproliferative disorders. It is possible that some variants included in this group are subject to environmental factors. However, such factors have not been clearly delineated.

Aetiology and Pathogenesis of Childhood Leukaemia and Lymphoma

(*i*) *Burkitt's lymphoma.*

It appears almost undisputable that environmental factors are responsible for the marked disparity in the incidence of BL in the endemic and non-endemic parts of the world. Recent studies[24 25] have more closely linked the aetiology of endemic BL with EBV infection. Although a role for holoendemic malaria has been postulated in the pathogenesis of BL, this does not appear to be a satisfactory explanation, since other parts of the world (eg Amazon Basin) where similar epidemiological situations of holoendemic malaria and high EBV infection rate coexist are without a comparable incidence of BL. It has, however, been suggested that chronic malarial infection leads to immunosuppression[26] and hyperproliferation of EBV transformed lymphocytes.

Since EBV and holoendemic malarial infection alone do not adequately explain the epidemiology of BL in Africa, it has been postulated that other aetiologic agents, for example, infection by papovavirus[27], may play an additional role. The recently described human retrovirus, human T-cell leukaemia/lymphoma virus (HTLV)[28 29], appears to be another potential agent in this respect. We have recently obtained evidence of high infection rate of this virus among Nigerians, including children, living in the south-western region of Nigeria[30]. Furthermore, HTLV-I sero-positivity was recently observed in association with various forms of childhood lymphoproliferative disorders (Table III) including BL in Ibadan. However, since HTLV is supposed to be T-lymphotropic, its association with a B-lymphoma may not be easily explainable. It is conceivable that infection at some early stages of life may lead to depletion of a subset of T-lymphocytes, thus leading to immunosuppression. Conversely, B-lymphocytes can be targets of this virus, as has recently been shown[28], with subsequent neoplastic mutation.

The "final pathway" in the pathogenesis of endemic and non-endemic BL is the specific chromosomal aberration whereby there occurs a translocation of genetic material from chromosome number 8 to chromosome 14, 22 or 2, thus, leading respectively to the following chromosomal changes: t(8;14), t(8;22) or t(8;2)[31]. This is believed to occur randomly, consequent upon uncontrolled proliferation of stimulated lymphocytes, thereby resulting in the transfer as well as the expression of a cancer associated gene, "c-myc gene", with eventual neoplastic transformation of the cell[32]. While it is likely that EBV is the initiator of the lymphoid proliferation in endemic BL, it is not clear what sets the abnormal proliferation into action in the non-endemic cases. The Figure represents the current thinking of the pathogenetic mechanism of Burkitt's lymphoma.

TABLE III

Confirmed HTLV-I Sero-positivity in Childhood Haematopoietic and other Malignancies in Ibadan

Disease	*No Tested*	*No Positive*	*%*
ALL	6	0	0.0
AML	2	1	50.0
BL	28	7	25.0
HD	2	0	0.0
NB/NHL	2	1*	50.0
Miscellaneous	2**	1***	50.0
Children without systemic disease or cancer	6	1	16.7

* : Histopathological and serological evidence of adult T-cell leukaemia-lymphoma (ATL)

** : One case each of Wilm's tumour and neuroblastoma

*** : Wilm's tumour

ALL : Acute lymphoblastic leukaemia

AML : Acute myelogenous leukaemia

BL : Burkitt's lymphoma

HD : Hodgkin's disease

NB/NHL : Non-Burkitt's, non-Hodgkin's lymphoma

(*ii*) *Acute leukaemia*

There are still no firm clues as to the aetiology and pathogenesis of the acute leukaemias. Viruses have long been known to be involved in the aetiology of animal leukaemia[33]. Consequent upon the recent discovery of a human retrovirus, the human T-cell lymphotropic virus (HTLV)[28 29], it now appears likely that, at least, some variants of human leukaemia are caused by viruses. As shown in Table III, some childhood leukaemias and lymphomas in Ibadan appear to be associated with HTLV infection. However, the role of the virus in the aetiology of these variants of childhood leukaemia/lymphoma is yet to be determined.

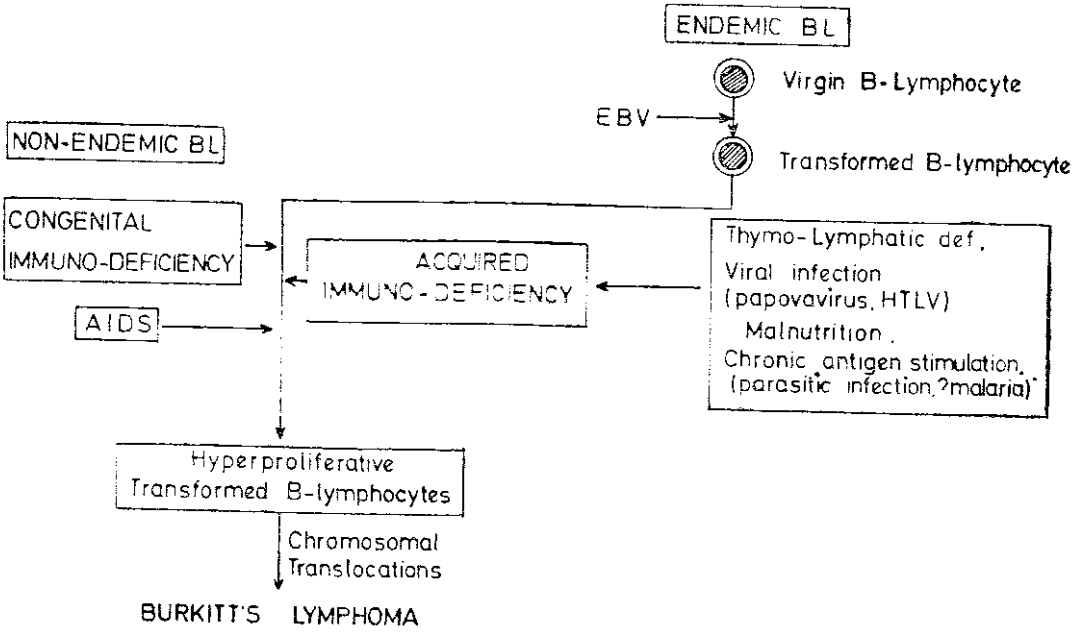

Fig . An hypothetic concept of the pathogenesis of "endemic" and "non—endemic" Burkitt's lymphoma

Conclusions

The most remarkable differences in the epidemiology of childhood neoplasia between the developing areas of Africa and the developed countries of Europe and North America involve the incidence rates of the acute leukaemias and the lymphoma. Reports from various parts of the world, some of which are reviewed in this paper, indicate that environmental factors are most likely responsible for these differences. Although various aspects of childhood acute leukaemia have been the subjects of extensive investigations in developed countries, scientific information on this form of disease in African children is very limited. The practice of paediatrics in most parts of Africa is inundated by preventable conditions like communicable diseases, malnutrition, and high rates of perinatal and infant mortality. The situation is further compounded by the scarcity of manpower in relevant fields of Medicine. Although the leukaemias do not constitute an appreciable community health problem in Africa, an understanding of their biology in our part of the world is likely to shed considerable light on the relation between environmental factors and regulation of haemopoiesis.

That childhood acute leukaemia is infrequently diagnosed in Africa has long been known[34]. However, the explanation of this situation by a suggestion of underdiagnosis[35 36] is probably fallacious and misleading. In fact, the situation whereby the incidence of ALL is low in the first two quinquennia and that of chloroma-associated AML is increased among Ibadan children compared to children in developed countries is reminiscent of the result of experiments in animal leukaemia. Thus, thymectomy in spontaneous-leukaemia bearing animals like AK or C3H mice causes a delay and reduction in number of cases of lymphoid leukaemia while

increasing the occurrence of chloroleukaemia[37]. This observation has led to a proposition of a hypothesis that the epidemiological features of childhood leukaemia in Africa probably represent Nature's equivalents of Gross' experiments[38] and are probably related to the thymolymphatic deficiency and acquired immuno-deficiency state that results from malnutrition[39 41] and other adverse occurrences of early stages of life. That suggestion can now be further extended to include an explanation of the inverse relationship in the incidence of ALL and BL in developing African countries and developed countries of Europe and North America (Table II).

If the hypothesis that has been advanced is a correct one, one would expect the epidemiological features of childhood leukaemia/lymphoma in Africa to evolve with time and with improvement in the socio-economic status of the people to a pattern more like that of economically more developed countries. However, for now, the existence of these epidemiological features represent a unique experiment of Nature and should provide us with an opportunity to study the influence of environmental factors in the pathogenesis of leukaemia and lymphoma.

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