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LEUKAEMIA AT QUEEN ELIZABETH CENTRAL HOSPITAL IN BLANTYRE, MALAWI
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LEUKAEMIA AT QUEEN ELIZABETH CENTRAL HOSPITAL IN BLANTYRE, MALAWI

J.M. MUKIIBI, C.M. NYIRENDA, J. O. ADEWUYI, E.L.B. MZULA, E.D. MAGOMBO and E.M. MBVUNDULA

ABSTRACT

Objectives: **To determine the patterns of leukaemias seen in Malawians at Queen Elizabeth Central Hospital (QECH) and to compare the findings with those from elsewhere. An overview of the problems encountered in the management of leukaemia in developing countries especially those in sub-Saharan Africa are highlighted.**

Design: **Retrospective descriptive analysis of consecutive leukaemia cases seen from January 1994 through December 1998.**

Results: **Of the 95 leukaemia patients diagnosed during the study period, childhood (0 - 15 years) leukaemia occurred in 27 (28.4%) patients while adulthood (above 15 years) leukaemia accounted for 68 (71.6%) patients. The main leukaemia types were: acute lymphoblastic leukaemia (ALL) 14 (14.7%), acute myeloblastic leukaemia (AML) 25 (26.3%), chronic myeloid (granulocytic) leukaemia (CML) 32 (33.7%), chronic lymphocytic (lymphatic) leukaemia (CLL) 22 (23.2%) and hairy cell leukaemia (HCL) two (2.1%) patients. Most of the acute leukaemia (AL) cases occurred in the six to 15 year age bracket with a male preponderance. In ALL, lymphadenopathy was the commonest presenting feature followed by pallor (92.9%) while in the AML group, pallor occurred in 80% of cases. Abdominal swelling (87.5%) due to splenomegaly (81.3%) were the main clinical features in the CML group whereas lymphadenopathy (63.6%) followed by splenomegaly (59.1%) were the dominant presenting features in CLL. Haematologically, although leucocytosis characterised both acute and chronic leukaemias, most cases of acute leukaemia presented with more severe anaemia (Hb<7g/dl) and marked thrombocytopenia (Platelet count <50 x 10^9/l) than the chronic leukaemias.**

Conclusions and recommendations: **The study shows that leukaemias are not rare in Malawi and cases which were diagnosed in this series probably only represent the tip of the iceberg. While there is need to increase diagnostic awareness among clinicians and laboratory staff, the severe chronic shortage of cytotoxic drugs and lack of supportive care facilities commonly encountered in developing countries should be realistically addressed through cost-sharing, cost recovery, adequate government subvention and donations from charitable organisations.**

INTRODUCTION

Most of the literature published in the 1950s and 1960s about malignant diseases in Africa, overemphasised the rarity of leukaemia in the indigenous African(1-3). However, a recent bibliography on leukaemias in Africa(1), though revealed ample documentation of the occurrence of leukaemias in most African countries, it disclosed a glaring absence of studies on leukaemias from Malawi. In a recent analysis of childhood cancers in Malawi (4), acute leukaemias surfaced as one of the top ten common paediatric malignant diseases. Recent studies from Africa and elsewhere in the world(5, 6) also provide further evidence that there is a true worldwide increase in the incidence of leukaemia. Furthermore, the changing presenting patterns, the variation in leukaemia distribution, response to therapy and prognosis that characterise some of the subtypes of leukaemias in the African setting merit further investigations as they may be of crucial importance in providing some of the missing aetiological clues(5). In view of these observations coupled with lack of a previous documentation on the subject from Malawi and the fact that new approaches to leukaemia aetiology rely heavily on an understanding of the biology of the types of leukaemia(6), it was felt necessary to conduct a study, first to establish the pattern and characteristic features of the

various types of leukaemias seen in Malawians; secondly to compare the findings especially with respect to age, sex, morphological type and clinical presentation with those from elsewhere in the world; and thirdly to highlight some of the problems encountered by physicians in management of leukaemia in a developing country like Malawi.

MATERIALS AND METHODS

The presenting clinical and haematological data of the patients diagnosed as having leukaemia during the period of January 1994 through December 1998 at Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi, were retrieved from the patients' clinical notes on to proformas for analysis. The diagnoses of the various types of leukaemias were based on peripheral blood counts, examinations of peripheral blood films and bone marrows including cytochemistry which was limited to Sudan Black (SB), Myeloperoxidase (MPO) and Periodic Acid Schiff (PAS) stains in cases of acute leukaemia. Standard haematological practice as described by Dacie and Lewis(7) was closely followed. Morphological classification was based on the French - American - British system by examining Giemsa stained blood and bone marrow smears(8 -11). In the case of acute lymphoblastic leukaemia a scoring system was used to differentiate between L1, L2 and L3 morphology(9). Response to therapy was defined by improvement in the observable clinical signs and symptoms as well as haematological profiles. The main factors which were taken into consideration included the morphological type of leukaemia, age, sex, presenting clinical and blood counts. The data was compared with that from other parts of the world.

RESULTS

During the five year period, 95 patients were diagnosed as having leukaemia of various types. Out of the ninety five, 56 (58.9%) were males and 39 (41.1%) females giving an overall male/female ratio of 1.4:1.

Type, age and sex distribution: This is summarised in Table 1. There were 39 patients with acute leukaemias and 56 cases were of chronic type. Out of the total of 95 cases, 27 (28.4%) occurred in childhood (0-15 years), while 68 (71.6%) were found in the adult age group (15 years and above). In the acute leukaemia (AL) group, acute myeloblastic leukaemia (AML) was found to be commoner than acute lymphoblastic leukaemia (ALL) with respective percentage incidences of 26.3 and 14.7; while in the chronic leukaemia (CL) group, chronic myeloid leukaemia (CML) was commoner than chronic lymphocytic leukaemia (CLL) with percentage incidences of 33.7 and 23.2 respectively. The age ranges for AL, CL and for all patients were 0.6 to 53 years, 10 to 77 year and 0.6 to 77 years respectively. Most cases of AL (48.7%) occurred in the six to fifteen age bracket while in the CL group the majority of cases (46.4%) presented after the fifth decade. A comparison of male/female ratios showed a male predominance for all types of leukaemias except for CLL and HCL where sex ratios were 0.8 and 1 respectively. Table 2 summarises series of leukaemia literature reviewed. Contrary to previous belief that the incidence of

Table 1

Type, age and sex distribution of the 95 leukaemia cases

Age group	ALL		AML		CML		CLL		HCL		Totals
	M	F	M	F	M	F	M	F	M	F	M + F (%)*
Childhood (0-15 yrs)	7	2	10	6	2	0	0	0	0	0	27 (28.4)
Adulthood (<15 yrs)	3	2	7	2	15	15	10	12	2	0	68 (71.6)
Totals: M + F	14		25		32		22		2		95 (100)
(%)*	(14.7)		(26.3)		(33.7)		(23.2)		(2.1)		(100.0)

Key: M=male; F = Female; *Figures in parentheses indicate percentages

Table 2

Percentage distribution of the 95 leukaemia cases in the present series compared with other series

Country	Authors	No.	AL (%)	CML (%)	CLL (%)	Others (%)
DRC (formerly Zaire)	Sonnet *et al*, 1966	35	54.3	20.0	25.7	0
Kenya	Kasili, 1978	256	56.1	28.5	15.4	0
Nigeria (UCH, Ibadan)	Essien, 1972; 1976	262	31.7	34.3	31.7	2.3
Nigeria (Northern)	Kulkarni, 1986	467	43.3	28.7	28.0	0
Sudan	Ahmed *et al*, 1982	256	42.2	42.5	13.3	2.0
Uganda	Lothe, 1967	88	52.3	29.5	18.2	0
Zambia	Fleming, 1988	50	64.0	26.0	10.0	0
Zimbabwe (formerly Rhodesia)	Lowe, 1974	95	48.4	34.8	16.8	0
South Africa (Whites)	Grieg, 1958	86	53.5	15.1	31.4	0
USA (Whites)	Wintrobe, 1981	565	57.0	19.5	23.5	0
Malawi*	Mukiibi *et al*, 1999	95	41.0	33.7	23.2	2.1

Key: No.=Number of patients; AL=Acute leukaemia; *=Present study

AL is generally lower in Africans than in Caucasians(2), the data under review shows that in four out of the nine African countries where leukaemia has been studied in indigenous Africans of all ages, the incidence of AL is very similar to that in white South Africans; though much lower when compared to American whites. With respect to CL, CML appears to be commoner in Africans while CLL is the commonest type in Europe and North America. The incidences of the different types of leukaemia in the present series conformed to the African pattern.

Presenting clinical features: These are shown in Tables 3 and 4. In the AL group, the main presenting symptoms for ALL were weakness (71.4%), headache (42.9%), fever (35.7%) and epistaxis (21.4%) and for AML were weakness (76%), headache (36%) and fever (32%). The commonest physical signs for ALL were lymphadenopathy (100%), anaemia (92.9%) and splenomegaly (14.3%) while those for AML were anaemia (80%), lymphadenopathy (32%), proptosis (24%) and chloromata (16%).

Table 3

Presenting clinical features in 39 cases of acute leukaemia

Clinical feature	ALL (n=14) No.	%	AML (n=25) No.	%
Symptoms				
Weakness/fatigue	10	71.4	19	76
Headache	6	42.9	9	36
Fever (on and off)	5	35.7	8	32
Epistaxis	3	21.4	3	12
Eye swelling	–	–	6	24
Bleeding gums	1	7.1	4	16
History of multiple blood transfusions	1	7.1	3	12
Bone and joint pains	1	7.1	2	8
Respiratory tract infection	–	–	2	8
Vomiting	1	7.1	–	–
Signs				
Pallor/anaemia	13	92.9	20	80
Lymphadenopathy	14	100	8	32
Proptosis	–	–	6	24
Splenomegaly	2	14.3	3	12
Chloromata	–	–	4	16
Bone tenderness	1	7.1	2	8
Hepatomegaly	1	7.1	1	4
Cardiac failure	1	7.1	–	–

In the CL group (Table 4), the commonest triad of symptoms for CML were abdominal swelling (87.5%), tiredness (53.1%) and fever (9.4%) and those for CLL were abdominal swelling (45.5%), weakness (54.5%) and fever (22.7%). The commonest physical signs for CML were splenomegaly (81.3%), anaemia (31.3%) and hepatomegaly (18.8%) and those for CLL were lymphadenopathy (63.6%), splenomegaly (59.1%) and pallor (22.7%).

Table 4

Presenting clinical features in 56 cases of chronic leukaemia

Clinical feature	CML (n=32) No.	%	CLL (n=22) No.	%	HCL (n=2) No.	%
Symptoms						
Abdominal swelling/ pain/discomfort	28	87.5	10	45.5	2	100
Tiredness/weakness	17	53.1	12	54.5	–	–
Fever (on and off)	3	9.4	5	22.7	2	100
Loss of weight	1	3.1	2	9.1	–	–
Signs						
Splenomegaly	26	81.3	13	59.1	2	100
Lymphadenopathy (Cervical/axillary/ inguinal)	5	15.6	14	63.6	–	–
Anaemia/pallor	10	31.3	5	22.7	2	100
Hepatomegaly	6	18.8	2	9.1	1	50
Cardiac failure	1	3.1	1	4.5	–	–
Ascites	1	3.1	1	4.5	–	–
Pleural effusion	1	3.1	–	–	–	–
Swollen, tender left calf muscles	1	3.1	–	–	–	–

Abdominal swelling, fever, splenomegaly and anaemia were present in the two patients who had HCL.

Presenting haematological features: For AL these are given in Tables 5 and 6 while for CL they are summarised in Table 7.

Table 5

Full blood counts in 39 cases of acute leukaemia at presentation

Blood count index	ALL (n=14) No.	%	AML (n=25) No.	%
Total Wbc count ($x10^9/l$)				
<10	–	–	2	8
10-99.9	5	35.7	17	68
100-300	9	64.3	6	24
Haemoglobin: (g/dl)				
<7	9	64.3	15	60
7-10	4	28.8	9	36
>10	1	7.1	1	4
Platelet count ($x10^9/l$)				
<50	6	42.9	15	60
50-100	3	21.4	3	12
>100	1	7.1	1	4

The range of Wbc count was 4.2 to $280x10^9/l$ with a mean ± s.d. of 88.8 ± 64.9. Hyperleucocytosis (wbc count >100) accounted for 64.3% and 24% of ALL and AML respectively. The range for Hb was 3.2 to 10.4 g/dl with a mean ± s.d. of 6.6 ± 1.7 while the range of platelet count was 8 to 120 x $10^9/l$ with a mean ± s.d. of 43 ± 29; severe anaemia (Hb<7) being found in 64.3% and 60% of ALL and AML respectively and severe thrombocytopenia (Platelet count <50 x $10^9/l$) accounting respectively for 42.9% and 60% of the ALL and AML.

In the ALL group (Table 6), L1 (57%) was the commonest subtype followed by L2 (36%) while for the AML group the commonest type was M4 (36%) followed by M5 (16%).

Table 6

FAB subtypes of the 39 acute leukaemia cases*

Age group	ALL (n=14) L1	L2	L3	AML (n=25) M0	M1	M2	M3	M4	M5	M6	M7
Childhood (0-15 yrs)	6	2	1	2	2	2	1	5	4	0	0
Adulthood (<15 yrs)	2	3	0	0	0	1	1	4	0	2	1
Totals	8	5	1	2	2	3	2	9	4	2	1
(%)**	(57)	(36)	(7)	(8)	(8)	(12)	(8)	(36)	(16)	(8)	(4)

Key: *FAB = French American British classification (7-10)
**Percentages of the subtypes of leukaemia according to the type of acute leukaemia

Table 7

Full blood counts in 56 cases of chronic leukaemia at presentation

Blood count index	CML (n=32) No.	%	CLL (n=22) No.	%	HCL (n=2) No.	%
Total Wbc ($x10^9$/-1)						
<10	-	-	-	-	2	100
10-99.9	7	21.9	10	45.5	-	-
100-300	17	53.1	9	40.9	-	-
>300	8	25	3	13.6	-	-
Haemoglobin (g/dl)						
<7	9	28.1	3	13.6	2	100
7-10	8	25	12	54.5	-	-
>10	15	46.9	7	31.8	-	-
Platelet count ($x10^9$/1)						
<50	-	-	-	-	1	50
50-99	-	-	2	9.1	1	50
100-400	17	53.1	14	63.6	-	-
>400	13	40.6	-	-	-	-

The range of Wbc count was 2.1 to 998 x 10^9/1; mean ± s.d 201.8 ± 183.8 (Table 7). The range of Hb was 3.5 to 14.7 g/dl; mean ± s.d. 8.9 ± 2.5 and the range of platelet count was 45 to 1006 x 10^9/1 with a mean ± S.D. of 319 ± 205. Hyperleucocytosis (Wbc count > 100) was found in 78.1% of CML and 54.5% of CLL. Severe anaemia (Hb < 7) was found in 28.1% of CML and in 13.6% of CLL. Severe thrombocytopenia (Platelet count < 50x10^9/1) was only observed in one patient with HCL while thrombocytosis (Platelet count > 400x10^9/1) was only seen in 40.6% of patients with CML.

Therapy: Various combination chemotherapeutic regimens were used but for only a few patients who could afford to buy the drugs on their own account. These were DOP (daunorubicin, oncovin and prednisone) or OP (oncovin and prednisone) for ALL; DAT (daunorubicin, cytosine arabinoside and thioguanine) for AML; busulphan or hydroxyurea or alpha -interferon for CML and chlorambucil for CLL. Supportive management consisted of blood transfusion and antibiotics whenever these were appropriately indicated.

Response to therapy and survival: Only 15 (15.8%) out of 95 patients could afford to procure drugs on their own account and were therefore the ones available for evaluation. Of these four had ALL, two had AML, six were CML and three had CLL. The majority of patients, 80 (84.2%), who could not afford the drugs were palliatively treated and later lost to follow up within three to four weeks of diagnosis. For those treated with cytotoxic drugs, in the AL category the initial response was, at best, partial in most cases. Only three out of four cases of ALL showed complete remission but this was followed by relapse and death at variable intervals over nine months of follow up. Two cases of AML failed to respond and died within the first month of follow up. In the CL group, the initial responses were followed by remissions and relapses. At the time of this presentation, two of the six cases of CML and two of the three cases of CLL were still alive after a total follow up of 63 months. Anaemia, haemorrhage, infection or a combination of these were the main causes of deaths.

DISCUSSION

Early investigators over-stressed the rarity of leukaemia in the indigenous African (2). It is possible that those early workers merely assumed that leukaemia was rare in the African or possibly they were pre-occupied with commoner infectious conditions that have long plagued tropical Africa. However, the problem of underdiagnosis(3) and the fact that there are few haematologists currently practising in tropical Africa may be the other contributing factors to the presumed low leukaemia incidence that has hitherto been alleged to occur in Africa. This study serves as evidence that leukaemia should no longer be considered a rare disease in Malawi. In western countries, ALL is frequent in childhood reaching a peak at three to four years while AML occurs in young adults and shows a proportionate increase with age. Contrary to these findings, AML was the commonest morphological leukaemia type in this study and accounted for 64% of childhood leukaemia just as previously reported for black children of African descent in the USA(13) as well as in East and Central Africa(14,15).

Chloromatous deposits which occurred in four (16%) patients with childhood AML is also comparable to figures

of 10% and 25% of African AML children presenting with chloromas(5). Another new and interesting finding which has not been exhaustively investigated was that M4 on the FAB classification accounted for 36% of all AML cases which was in keeping with a figure of 35% recently reported for M4 in Zimbabwe (16). However, with regard to ALL, L1 accounted for 57% of ALL cases contrasting with the Zimbabwean experience where L2 was found in 69% of ALL cases(16). Moderate to severe pallor was the commonest presenting sign in the AL group accounting for 92.9% of the ALL and 80% of the AML cases. Although severe thrombo- cytopenia (Platelet count <50 x 10^9/l) was found in 42.9% of ALL and in 60% of AML, serious mucosal bleeding manifestations were not observed. The explanation for this is not clear and is currently being further investigated.

Sex ratio: The finding of a male predominance with an overall male/female ratio of 1.4:1 for all types of leukaemias correlates closely with the African (1-3, 14-16) and western (6, 12) countries.

Age distribution: Early reports published in the 1960s and 1970s from Africa emphasised the rarity of leukaemia under five years(1,2) compared to the experience in the western hemisphere(12). However, recent studies from Africa(1,14-17) show that leukaemia occurs in the first five years of life as it is the case in western countries(12). In this series only six (15.4%) of all AL patients were below five years with AML being more common than ALL. As in other African series(1), CML was commonest in the third and fourth decades compared to the Western populations where it peaks in the fifth decade (6, 12) although this may be a reflection of the age structures of the African versus Western populations (15,17). For CLL, although the peak incidence was in the sixth decade which is closer to the Western pattern, the disease was seen in young women below 45 years while above that age men were more commonly affected thus contrasting with the experience in the Western hemisphere (12).

Type of leukaemia: The present study which is in agreement with other African studies(1,3,4,14,16) shows that AL predominates and accounted for 41%, CML 37.7%, CLL 23.2% and HCL 2.1%. However, from the literature review (Table 2), it is evident that the proportion of acute to chronic forms of leukaemia in some African countries like Nigeria, Sudan, Zimbabwe and Malawi is lower than that expected from Western countries although most of the populations in those countries are well below the usual range for chronic forms of leukaemia. These differences may be a reflection of the type of population studied and whether children were included.

Presenting clinical and haematological features: Acute leukaemias were characterised by moderate (Hb 7-9.9g/dl) to severe (Hb < 7g/dl), anaemia, moderate (Wbc = 50-99.9 x 10^9/l) to severe (Wbc = 100 - 300 x 10^9/l) hyperleucocytosis and profound thrombocytopenia (Platelet count = <50 x 10^9/l); all of which are poor prognostic factors in African and Western series. For the CL group, anaemia was mild (Hb = 10 - 12g/dl) to moderate (Hb = 7 - 9.9g/dl) degree and this was associated with severe (Wbc >100 x 10^9/l) hyperleucocytosis and thrombocytosis (Platelet count >400 x 10^9/l) which occurred mostly in CML just as described in Western populations(12). Where splenomegaly which occurred in 81.3% of CML and 59.1% of CLL was associated with lymphadenopathy which was recorded in 15.6% of CML and 63.3% of CLL the prognosis was generally poor.

Management, response to therapy and survival: The most frustrating exercise is in the area of management of patients with leukaemia especially in a developing country where the cost of cytotoxic drugs is well beyond what most patients can afford to pay. Worse still, most African government referral hospitals suffer from chronic severe shortage of cytotoxic drugs and gross lack of supportive care facilities which makes successful management and follow up of leukaemia cases a total mockery. In this study, the majority of patients (84.2%) could not afford cytotoxic drugs and even the 15 (15.8%) patients who could afford to buy cytotoxic drugs, the response was poor as the drug supplies were erratic, interrupted or even stopped abruptly.

Additionally, a notable observation with the CML group is the fact that treatment with conventional drugs like busulphan and hydroxyurea only ameliorates the signs and symptoms of the disease and does not improve survival. Onwukeme (18) has discussed in detail the problems related to management of malignancies in general in the developing world. In Malawi some of the major constraints include: limited diagnostic facilities, chronic shortage of cytotoxic drugs, lack of adequate medical and nursing personnel, lack of supportive care facilities and long distances patients have to travel to reach central referral hospitals. Tangible solutions lie in cost sharing, cost recovery, adequate government subvention and provision of adequate material and human resources in addition to donations from charitable organisations. It is only when all these measures are adequately addressed and seriously implemented that patients presenting with leukaemia in any developing country like Malawi will have any real hope of survival.

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Letters to the Editor-in-Chief

Dear Sir,

Re: Left-handedness as a risk factor for head injuries (*East Afr. Med. J.* 2001; 78:22-24)

I wish to congratulate the authors for this interesting appraisal of the proness of (left) handed drivers to road traffic accidents (RTAs) resulting in head injuries. However, in the article I have not read any mention of "eye/dominance" in these individuals. It is well known that we have a dominant eye and if there is a discrepancy between the two dominant factors, that is, a dominant (left) eye in a (right) handed person or vice versa, that individual may have episodes of minor dyspraxia.

Could it be that a fair percentage of "sinistrals" are in fact (right) eyed in which case these would be an added risk factor.

Yours faithfully,

A.P. Landra, MS, FRCS, Plastic Surgeon, The Nairobi Hospital, P.O. Box 56854, Nairobi, Kenya

This letter was forwarded to the authors of the article in question for comment and their reply is as follows:

Dear Sir,

Re: Left-handedness as a risk factor for head injuries (*East Afr. Med. J.* 2001; 78:22-24)

We are grateful to Dr Landra for raising a question on association between handedness and eyedness and the possible effect of discrepancy between the two sidedness on traumatisation rate. We analysed handedness in trauma patients because evaluation of it renders consistent results while methods for detection of eyedness are less reliable(1).

According to literature(1), other parameters of sidedness, such as eye, foot and ear preference are generally correlate with handedness in right-handers but they do not improve prediction of cerebral lateralisation based on hand preference. A recent study(2) demonstrated that non-right-handed individuals have reduced rather than reversed asymmetry for foot, ear and eye preference. Therefore, it is unlikely that a fair proportion of left-handers was right-eyed in our study.

Yours faithfully

Y. Zverev, MD, PhD, Department of Physiology and A. Adeloye, FRCS, FRCP, Department of Surgery, College of Medicine, University of Malawi, Private Bag 360, Chichiri, Blantyre 3, Malawi

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2. Polemikos, N. and Papaeliou, C. Sidedness preference as an index of organisation of laterality. *Percept. Mot. Skills.* 2000: **91**:1083-1090.