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Prospective studies on Hodgkin's disease in Ibadan — a preliminary report

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Summary

A preliminary report of a prospective study of Hodgkin's disease (HD) is provided, based on clinical and laboratory findings on 21 patients seen between July 1978 and December 1979 at the University College Hospital (UCH), Ibadan. Staging procedure was minimized to relatively simple surgical procedures like lymphangiography and percutaneous biopsy. Staging laparotomy was performed only in one case. Female patients were significantly older than males ($P < 0.05$). Patients with lymphadenopathy were significantly older than those without ($P < 0.05$), while those with systemic symptoms were significantly younger than those without. Eighteen (86%) of the patients presented with stage IV disease while 12 (57%) had the unfavourable histologic 'mixed cellularity' or 'lymphocyte depleted' variants. Systemic symptoms were present in 16 (76%) of patients. Fifty-three % of adequately treated patients showed poor response to chemotherapy. The prognosis of HD in Ibadan is on the whole unfavourable. A delineation of the prognostic factors is indicated.

Résumé

Nous présentons ici un rapport préliminaire d'une étude prospective de la Maladie de Hodgkin (MH) basée sur les manifestations cliniques et les résultats de laboratoire chez 21 malades suivis au Centre Hospitalier Universitaire (CHU) d'Ibadan entre Juillet 1978 et Décembre 1979. La détermination du stage clinique fut limitée à des interventions chirurgicales telles relativement simples tel que la lymphangiographie et la biopsie percutanée. Dans un seul cas fut effectivée une laparotomie à fin de determiner le stage de la maladie. Les malades de sexe féminin se sont révelées plus agées que ceux de sexe masculin différence statistiquement significative ($P < 0.05$). Les patients avec une lymphadenopathie étaient statistiquement plus vieux que ceux n'en presentant pas ($P < 0.05$) tandis que ceux avec des symptômes systémiques plus jeunes ($P < 0.05$). Dix-huit malades sur vingt-et-un (18/21) (86%) se sont présentés au stage IV de la maladie tandis que 12/21 (57%) avaient des formes histologiques défavorables: 'mixed cellularity' ou 'lymphocyte depletion'. La majorité (76%) des malades avaient des symptomes systémiques. Dans la groupe des malades traités de façon adéquate, 53% ont montré une mauvaise réponse à la chimiothérapie. Le pronostic de la MH à Ibadan est défavorable en général. Mention est faite de facteurs influençant le pronostic.

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Introduction

The manifestations of Hodgkin's disease as seen in Nigeria have been previously described in a number of reports. Some of these reports were based on clinico-pathological analysis of surgical biopsy and post-mortem materials (Edington & Hendrickse, 1973; Edington, Osunkoya & Hendrickse, 1973) while others have made an attempt to portray the clinical aspects of the disease as seen in Ibadan (Onyewotu, Francis & Montefiore, 1972; Oluboyede & Esan, 1976). The two clinical and the two clinico-pathological reports were based on retrospective analyses; they could therefore be expected to suffer from limitations that are characteristic of studies of that nature. Olweny *et al.* (1971), and Ziegler *et al.* (1972) reported

on their prospective studies of Hodgkin's disease in Ugandans and some of their findings were similar to those in the Nigerian studies. These findings include (i) prevalence of the prognostically adverse histologic types; (ii) presentation at advanced stages of the disease and (iii) unusual aggressiveness of the disease among the two African populations. While the Ugandan reports emphasized the increased incidence of the disease among children, the Nigerian reports, with the exception of that of Edington, Osunkoya and Hendrickse (1973), were silent on this aspect of Hodgkin's disease in Nigeria. Furthermore, the data on treatment of Hodgkin's disease in Nigeria is scanty.

It is clear from this information that in order to make a valid comparison of the clinical behaviour of Hodgkin's disease, as seen in Ibadan and other parts of the world, an analysis of our prospective experience is likely to be more fruitful than hitherto. The following is a preliminary report of an on-going prospective study of patients with Hodgkin's disease in Ibadan.

Materials and methods

Beginning in July 1978, a prospective study of cases of Hodgkin's disease diagnosed by or referred to the Department of Haematology, UCH, Ibadan was embarked upon with a view, amongst other things, to identify prognostic factors that characterize Hodgkin's disease in Ibadan, and to determine the response to a uniform treatment regimen. Some of these referrals were made from various departments for the purpose of chemotherapy following the confirmation of an initial clinical impression of Hodgkin's disease by a histological diagnosis. Other cases were referred from other departments of the hospital or extraneous sources to the Department of Haematology for investigation of lymphadenopathy and/or hepatosplenomegaly associated with or without systemic symptoms such as weight-loss, fever or night sweats. Many of the latter type of cases had undergone prolonged investigation, and in some cases even therapeutic trials for tuberculosis which had not been confirmed in many of the cases.

Management

Chemotherapy. All patients were treated uniformly with a regimen of combination of agents using the principles and schedules earlier described by De Vita, Serpick and Carbone (1970), but with some modifications, e.g. mechlorethamine was not available and had to be replaced by cyclophosphamide. Thus, they received cyclophosphamide 650 mg/m^2 and vincristine 1.5 mg/m^2 intravenously on days 1 and 8; and procarbazine and prednisolone, 100 mg/m^2 and 40 mg/m^2 orally, daily respectively from day 1 to day 14 of a 28-day cycle. The following course was started on day 29 of the preceding cycle, but occasionally the treatment was delayed either because of difficulty in drug delivery or failure of patient to keep his appointment. In case of persistent cytopaenia, the doses of cyclophosphamide and procarbazine were reduced according to a sliding scale or omitted if white blood cell count was $\leq$ 1500/cm^2 or platelet count was $\leq$ 50,000/cm^2.

Staging procedure

Patients were clinically staged mainly according to the recommendation contained in the reports of two international committees on the criteria of clinical staging and classification of Hodgkin's disease (Rosenberg, 1966; Carbonne *et al.*, 1971). The classification as reported by Lukes *et al.* (1966) was adopted for histological subtyping into: (1) lymphocyte predominance, (2) nodular sclerosis, (3) mixed cellularity and (4) lymphocyte depletion variants. The approach to staging of the disease in this group of patients was to use the least traumatic procedures to obtain relevant information rapidly, with respect to the extent of disease. Thus, staging laparotomy was discouraged while blind percutaneous biopsies were encouraged. Apart from the findings on physical examinations, further information with relevance to staging was obtained from liver function tests, bone marrow cytology and liver biopsy. During the period of study, owing to shortage of man-power it was not possible to obtain lymphangiographic studies regularly. Hence, it is likely that a few patients might have been understaged (e.g. staged as II instead of III) but, by and large, we believe that the modified staging procedure was adequate in the management of patients under the prevailing local conditions.

One of the patients had been splenectomized

for 'staging purposes' before being referred to us. But apart from removal of the enlarged spleen, which was positive for HD, no other tissue had been biopsied, thus making him probable stage III. Three other patients were splenectomized in the course of investigation of the aetiology of hepato-splenomegaly. These patients were also appropriately surgically staged in anticipation of an eventual diagnosis of HD.

Two patients who presented with paraplegia were investigated with myelography and one of them had laminectomy and surgical decompression of the spinal cord.

Response to chemotherapy

Chemotherapy is said to lead to complete remission (CR) if complete disappearance of all enlarged lymphnode and reversal of hepato-splenomegaly as well as systemic symptoms is observed. Partial remission (PR) is the state of incomplete resolution of these findings and signs. The disease is said to have been unresponsive to chemotherapy if palpable masses or enlarged organs have shown reduction in size to less than half of original measurements between two treatment cycles. The duration of remission is measured from the time that the reversal is documented to the time of reappearance of palpable masses and/or systemic symptoms attributable to recurrent disease.

Results

There were fourteen male and eight female patients and their ages ranged from 7–52 years. The pattern of age distribution is shown in Fig. 1. The female patients were significantly older than the male patients, their mean ages ± s.e. being 30.6 ± 6.4 and 17.9 ± 2.7 years respectively ($P < 0.05$). Table 1 shows the most common clinical features at presentation. Lymphadenopathy was marked (i.e. > 0.5 cm in diameter) in nine and insignificant in twelve patients; the patients with marked lymphadenopathy were significantly older than those without, their mean ages ± s.e. being 29.7 ± 17.00

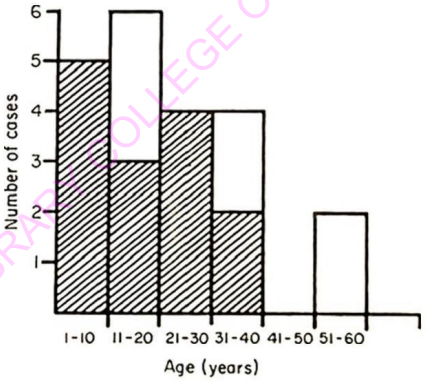

Fig. 1. Distribution of age in decades and sex of patients. ▨, male; □, female.

Table 1. Clinical features at presentation

Clinical features	No. of patients	Age of patients mean	s.e.	*P*-value
Lymphadenopathy — marked	9	29.67	16.96	<0.05
Lymphadenopathy — not marked	12	16.58	2.33	
Spleen 0–5 cm BLCM	12	24.50	4.74	>0.05
Spleen >5 cm BLCM	9	19.00	3.07	
Systemic symptoms — present	16	18.69	3.18	<0.05
— absent	5	33.20	5.35	
Nutritional state — good	8	33.75	4.89	<0.05
— poor	13	15.00	2.14	

BLCM = Below the left costal margin.

and 16.6 ± 2.3 years respectively ($P < 0.05$). Splenomegaly was marked (i.e. > 5 cm below the left costal margin) in nine patients and was absent or less than 5 cm below the left costal margin in twelve patients. There was no significant age difference between those with marked and less marked or no splenomegaly, their mean ages ± s.e. being 19.0 ± 3.0 and 24.5 ± 4.7 years ($P > 0.05$). Sixteen patients presented with systemic symptoms (fever of unknown origin, weight loss etc) while 5 patients were asymptomatic. Those with systemic symptoms were significantly younger than those without them, their mean ages ± s.e. being 18.69 ± 3.2 and 33.2 ± 5.4 years ($P < 0.05$). The nutritional state, as judged by weight and general physical findings, was judged to be poor in thirteen patients, some of whom presented in a state of cachexia (see Fig. 2), while eight patients were in good nutritional state. Patients in good nutritional state were significantly older than those in poor nutritional state, their mean ages ± s.e. being 33.8 ± 4.9 and 15 ± 2.1 years respectively ($P < 0.05$). Thus, patients without significant lymphadenopathy, but with systemic symptoms and poor nutritional state were more likely to be below the age of 20 years rather than above the age limit.

Histologic types and age

There were two cases of lymphocyte predominant, five of nodular sclerosis, eight of mixed cellularity and four of lymphocyte depleted histologic variants. Table 2 shows the relationship between the ages of the patients and the various histologic types. Nodular sclerosis and lymphocyte depleted types appear to be more frequently encountered in the younger age group, the mean ages of the patients with these two histologic types being 15.8 and 19.5 years respectively. The two patients with lymphocyte predominance had a mean age of 38.5 years, while the eight patients with mixed cellularity had a mean age of 24.2 years.

State of disease and age

Eighteen of the twenty-one patients had stage IV while two others had stage III disease. The remaining one patient was judged to have stage I. Patients with stages III and IV disease had

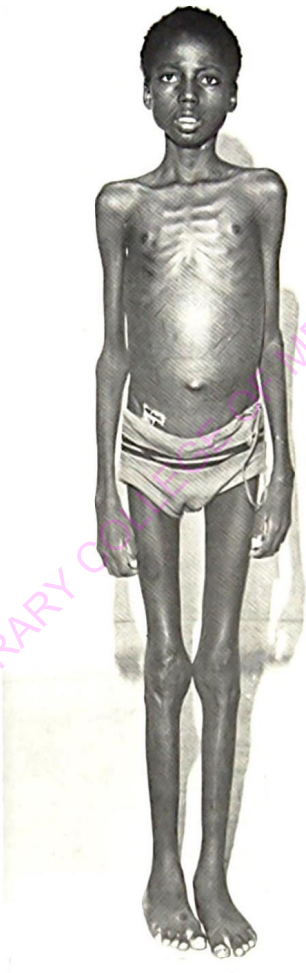

Fig. 2. Twelve-year-old boy with Hodgkin's disease clinical stage IVB. Note absence of gross adenopathy but gross hepatosplenomegaly and cachexia.

mean ages of 31.0 and 20.0 years respectively while the oldest patient in this series, a 52-year-old woman, was the only patient with stage I disease. Stage IV disease was diagnosed on account of involvement of the liver in thirteen, the liver and bone marrow in three, duraleptomeninges in two and the pleura in one case (see Table 3). There was no case of bone marrow involvement without liver involvement but most cases with evidence of liver involve-

Table 2. Histologic types* and age

Histologic type	No. of patients	Age range	mean
Lymphocyte predominance	2	25–52	38.5
Nodular sclerosis	5	9–36	15.8
Mixed cellularity	8	7–51	24.2
Lymphocyte depleted	4	13–25	19.5

*According to Lukes *et al.* (1966).

Table 3. Organ of involvement in stage IV disease

Organ/tissue	No. of patients	Age range	Mean
Liver	13	7–51	19.5
Liver with bone marrow involved	3	12–22	17.3
Bone marrow without liver involved	0	—	—
Dura/leptomeninges	2	24–36	30
Pleura	1	32	—

ment were without bone marrow involvement. Thus, the establishment of bone marrow involvement appears to signify a high degree of extensive disease.

Response to treatment and prognosis

Following an observation period of 8–15 months, the response to treatment of seventeen of the twenty-one patients was considered evaluable, the four others having either not been followed long enough or were lost to follow up. Five (29%) of the patients, died within the first 30 days of management. Of these, two died of progressive disease while others developed complications like infection (two cases) and diarrhoea of unknown aetiology (one case). Of the remaining twelve evaluable patients, eleven attained complete remission while one achieved partial remission. Remission duration was less than 6 months in four patients while the remaining eight patients had been in remission in excess of 8 months at the time of this report. Thus, of seventeen evaluable patients, only eight (47%) experienced a satisfactory control of their disease judged by the fact that they were disease-free at or beyond 8 months. The quality of disease control in the remaining nine (53%) patients can be described as poor. In an effort to identify possible factors responsible for the prognostic pattern observed in this small series of patients, we examined the influence of age of the patient and the nature of presentation — i.e. presence or absence of systemic symptoms at presentation. The mean ages respectively of patients with good and poor quality of disease control were 24.5 ± 15.4 and 19.60 ± 10.25 ($P > 0.05$). Thus, age did not appear to be a prognostic factor in this group of patients. However, among patients with good prognosis, systemic symptoms were present in half and absent in half while in the poor prognosis group, eight of the nine patients presented with systemic symptoms. Thus, the presence of systemic symptoms appears to correlate with poor prognosis, although it does not rule out a favourable

'good' prognosis as defined for the preliminary evaluation of this study.

Discussion

The fulminant nature of Hodgkin's disease as seen in Ibadan has previously been reported. Thus, Onyewotu *et al.* (1972) observed an overall mean duration of survival of less than 40 weeks irrespective of the type of treatment given. Edington *et al.* (1973) also presented clinico-pathologic evidence of rapidity of progression of the disease. Olweny *et al.* (1971) and Ziegler *et al.* (1972), using a standard chemotherapeutic regimen in a prospective fashion, have provided evidence that, when adequately managed, adult Ugandan patients did just as well, and Ugandan children with Hodgkin's disease did even better than their counterparts reported from Europe and U.S.A.

The results presented in this report are suggestive of an aggressive nature of Hodgkin's disease in Ibadan in that five (29.4%) of the seventeen evaluable patients died before the 30th day of management and of the remaining twelve (70.6%) patients, all of whom received a uniform combination chemotherapy, only eight (66.7%) were in remission at or beyond 8 months. Thus, nine of seventeen (53%) adequately managed patients showed poor control of their disease. The reason for this may be partly due to the fact that nitrogen mustard was not available and had to be replaced by cyclophosphamide. Our patients were, therefore, unable to benefit from the all-time best chemotherapeutic program known for the management of Hodgkin's disease (De Vita *et al.*, 1976). However, other reasons including extremely advanced stage of disease and possibly a chemotherapeutically less responsive disease may also be responsible for this discouraging result.

Other results observed so far in the study agree in general with what has been previously reported. Thus, we have observed the usual male predominance. In fact, in this series, it appears that Hodgkin's disease in Ibadan is a disease of young males and that the older the patient (i.e. > 40 years) the more likely the patient will be female. Patients at or below the age of 15 years (i.e. children) make up 42.7% of the whole group. Of all the previous reports from Ibadan only that of Edington *et al.* (1973) observed with 33% a similar relatively high incidence in childhood. However, the high childhood incidence observed in this study is consistent with those of Ziegler *et al.* (1972) and Burn *et al.* (1971). In fact, according to Guttensohn and Cole (1977), there is a correlation between the state of economic development of a nation and the incidence of childhood Hodgkin's disease. The reason for this will probably not be known until the cause of Hodgkin's disease is identified. However, Vianna and Polan (1978) have speculated on the role of viral agent of low virulence.

We could not identify a relationship between age and prognosis although young age appeared to be associated with lesser degree of lymphadenopathy and with the presence of systemic symptoms. Furthermore, the presence of systemic symptoms appears to be an important prognostic factor.

The number of patients presented in this preliminary evaluation of an on-going study is still too small to allow valid statements to be made on the peculiar behaviour of Hodgkin's disease in Ibadan. However, certain interesting trends are recognizable which have not been hitherto recognized. It will be interesting to see if the trends remain after more patients have been studied.

The decision to move away from the usual practice of surgical staging was taken for many reasons. The most important among these is that the procedure is irrelevant for Ibadan where radiotherapy is not available and where, therefore, all stages of the disease are treated with chemotherapy. Furthermore, the decision to perform splenectomy in an environment plagued with infectious conditions and where medical care is not easy to find should not be taken lightly. It appears that in view of the complications of surgical staging procedure there is now an increasing tendency in the developed countries to do less aggressive staging procedure (Desforges, Rutherford & Pino, 1979).

The problem of Hodgkin's disease as seen in Ibadan is, therefore, not limited to diagnosis only but also involves the question of appropriate management. While it is wise to observe some international guidelines in this regard, local modifications will be essential to meet local challenges.

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