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Neurological Manifestations of Burkitt's Lymphoma in Ghana

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Summary. Over a period of 2¼ years, seventy-five patients with histologically confirmed Burkitt's lymphoma were evaluated at the Korle Bu Teaching Hospital in Accra. Twenty-five patients (33%) presented or developed evidence of central nervous system involvement. Neurological abnormalities included paraplegia. cranial neuropathy, peripheral and root neuropathy, headaches and altered consciousness. Malignant pleocytosis was present or subsequently developed in twenty-four patients. Intrathecal methotrexate transiently reversed the malignant pleocytosis, without influencing the ultimate course of the disease appreciably in most of the patients. Survival among these twenty-five patients was poor compared to patients who did not develop CNS involvement.

Résumé. Sur une période de deux ans un quart, 75 malades atteints de lymphome de Burkitt histologiquement confirmé ont été evalues à la Korle Bu Teaching Hospital d'Accra. 25 malades (33%) présentaient ou ont présenté des complications du SNC. Les anomalies neurologiques comportaient la paraplégie, la neuropathie crânienne, la neuropathie périphérique ou profonde, la céphalalgie et des troubles de la conscience. La pléocytose maligne était présente ou s'est manifestée ultérieurement chez 24 malades. La méthotrexate intrathécale a renversé momentanément la pléocytose maligne sans influencer appréciallement, chez la plupart des malades, le cours ultime de la maladie. La survie chez ces 25 malades a été fiable par rapport aux malades sans complications neurologiques.

The involvement of the central nervous system (CNS) in Burkitt's lymphoma must now be a fairly well established clinical entity to physicians taking care of patients with this disease. However, very few prospective studies have been published describing in detail the clinical neurological manifestations associated with CNS involvement in Burkitt's lymphoma (Ziegler, 1970).

Over a period of 2¼ years, seventy-five histologically and/or cytologically confirmed

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Burkitt's lymphoma (BL) patients were evaluated in a prospective manner at the Korle Bu Teaching Hospital in Accra. Twenty-five patients (33%) had neurological abnormalities which were either present on initial admission or developed during the course of the disease. These patients form the basis of the present report. All patients included in this series were referred from various regions of Ghana to a special Burkitt's lymphoma clinic within the department of Child Health. None of the patients evaluated had received prior chemotherapy and after discharge were subsequently followed up at frequent intervals. Terminal patients were allowed to be taken home if parents so desired or insisted. In such cases, a medical social worker visited the patients regularly until their demise.

On admission a histological and/or cytological diagnosis of Burkitt's lymphoma was made on each patient according to the criteria established by the World Health Organization (1969). Cerebrospinal fluid (CSF) was examined for malignant cells routinely on each patient on admission, prior to discharge and thereafter whenever clinical signs (cranial, root/peripheral neuropathies, headaches, altered consciousness, convulsions, paraplegia) suggested possible CNS involvement. All patients were classified on first admission according to the four clinical stages outlined in Table 1.

TABLE 1. Clinical staging of Burkitt's lymphoma

Stage	Extent of disease
I	Single facial tumour mass
II	Two or more separate facial tumour masses
III	Intrathoracic, intra abdominal, paraspinal, or osseous tumour (excluding facial bones)
IV	Central nervous system (malignant cells in the CSF) or bone marrow involvement

TREATMENT

A standardized treatment schedule was used for all evaluated patients. Cyclophosphamide, 40 mg/kg i.v., was administered to each patient when the diagnosis of Burkitt's lymphoma was histologically or cytologically confirmed. This dose was repeated every 2 weeks, WBC counts permitting, for a minimum of four doses. Allopurinol was given for 10 days following each dose of cyclophosphamide. Patients who responded only partially or not at all to cyclophosphamide, either initially or on relapse, were treated with vincristine sulphate, 1·4 mg/m^2 i.v. on day 1, and methotrexate, 15 mg/m^2, p.o. days 1–4. If there was no response, cytosine arabinoside, 250 mg/m^2, was administered in 24 hr infusions for 3 days. Patients with malignant cells in the CSF, on initial admission or any time thereafter, were treated with intrathecal (i.t.) methotrexate, 10 mg weekly for a minimum of four courses, or until tumour cells disappeared from the CSF. Citrovorum factor was given to prevent systemic toxicity

RESULTS

The twenty-five patients with Burkitt's lymphoma who had neurological abnormalities can be divided into two major categories: those who presented with neurological abnormalities

on initial admission and those who developed neurological abnormalities after initial diagnosis and beginning of treatment.

Patients presenting with neurological abnormalities on initial admission

Twelve patients presented with neurological abnormalities on initial admission. Five of them presented with paraplegia, all of whom had flaccid paralysis with absent deep tendon reflexes. Two had urinary incontinence, sensory deficits and accompanying bed sores. Three of the five paraplegic patients presented with abdominal and facial tumours, one with abdominal tumour alone, and one with paraspinal tumour (surgical exploration).

Eleven of the twelve patients had increased cells in the CSF. Malignant cells or blastiocytes were identified in each of these patients. The only patient in this group who did not show this abnormality, but was paraplegic, developed malignant pleocytosis $6\frac{1}{2}$ weeks after admission. The number of cells in the CSF of patients with pleocytosis varied considerably and ranged from 18 to 1442 cells/mm^3. CSF protein content was generally elevated and the highest values were encountered in patients presenting with paraplegia. There was no correlation between CSF cell count and the protein content.

TABLE 2. Neurological abnormalities in twelve BL patients presenting with CNS involvement

Neurological abnormality	No. of patients
Paraplegia	5
Cranial neuropathy	2
Root/peripheral neuropathy	0
Altered consciousness	2
Headaches	1
Asymptomatic	5
CSF malignant pleocytosis	11

Five patients who presented with tumour cells in the CSF on admission were clinically asymptomatic, i.e. free of any neurological symptoms. The diagnosis of CNS involvement was established in these patients as a direct result of routine cytological examination of the CSF on all patients with BL on admission and before treatment. The frequency of other neurological abnormalities is shown in Table 2. Cranial neuropathy occurred in two patients: in one, extraocular muscles were involved; and in the other, multiple cranial nerves. Two patients presented with altered consciousness and one patient with severe headaches as a major neurological symptom. All patients who presented with CNS abnormalities had tumour elsewhere, with no correlation between sites of tumour and CNS involvement.

Patients developing neurological abnormalities

Of the fifty-six histologically confirmed and treated BL patients, who on initial admission presented with no evidence of CNS involvement, thirteen subsequently developed neurological abnormalities.

They include eight patients in stage III (abdominal tumours) and five in stages I–II (facial tumours). Of the eight stage III patients, five had both facial and abdominal tumours. The

neurological abnormalities manifested by this group of patients are summarized in Table 3. The high incidence of cranial (9/13) and root/peripheral (8/13) neuropathies in this group of patients was striking. The cranial nerves most commonly involved were the tenth (seven patients), the third (six patients), the sixth (four patients), the seventh (four patients), the fourth (two patients), the fifth (two patients), and the second, the eighth, and the twelfth (one patient each). Root/peripheral neuropathy principally involved the upper extremities (six patients) and clinically manifested itself as severe pains in the neck, shoulders and arms, accompanied by muscle weakness and diminished deep tendon reflexes. Two patients experienced root pains in the lower extremities, one of whom also had marked hyperaesthesia. She was the only patient who had received vincristine sulphate for treatment in this group. We believe that these root manifestations reflect infiltration of involved nerve roots

TABLE 3. Neurological abnormalities in thirteen BL patients developing CNS involvement

Stage	No. of patients	Paraplegia	Cranial neuropathy	Root/Peri. neuropathy	Altered consciousness	Headaches	Asympto-matic	Malignant pleocytosis
I–II	5	2	3	3	2	2	0	4*
III	8	2	6	5	1	4	0	8
Total	13	4	9	8	3	6	0	12

* CSF not examined in one patient (K-142).

by tumour cells extending from dural infiltrations. Severe headache was a common finding in patients developing CNS involvement and featured prominently in six patients. Papilloedema, however, was not observed in any of these patients. Four patients developed paraplegia, one with double incontinence and sensory loss and the other three with motor loss only. All patients in this group who subsequently developed CNS involvement had pleocytosis; malignant cells or blastiocytes were identified in the CSF from each of them. CSF cells counts varied greatly from patient to patient, ranging between 67 and 2226/mm^3. CSF protein was raised over 100 mg/100 ml in all patients except one, in whom it was normal. The cell count and the protein level bore no correlation with neurological symptoms.

Eight of the patients in this group developed CNS involvement while receiving systemic treatment for tumour at some other site. Two of the eight were receiving treatment for recurrent tumour (after previous complete remissions) when they developed CNS involvement. Three developed CNS involvement while they were completely free of tumour elsewhere, i.e. in complete remission. In two patients, tumour relapse and CNS involvement occurred simultaneously.

The time interval between beginning of systemic treatment and the development of CNS abnormalities varied considerably among these patients and ranged from 6 weeks to as long as 79 weeks. However, the majority (11/13) developed their neurological abnormalities between the sixth and eighteenth week after onset of systemic treatment.

Response to therapy and survival

Twenty-two patients, who either presented or developed neurological abnormalities, received combined i.t. methotrexate and systemic chemotherapy. Complete remission of malignant pleocytosis was obtained in all patients who received this combined therapy.

However, the remission of pleocytosis did not influence the prognosis in these patients. Most patients had an early CSF relapse, usually less than 6 weeks from time of normalization of the CSF cell count. Four patients presenting with, and three patients developing paraplegia, showed considerable improvement after therapy. However, residual neurological deficits remained in all of them. Patients presenting or developing cranial and/or root neuropathies generally showed considerable improvement, and, in many normal function was re-established after the combined systemic and intrathecal therapy. The general clinical

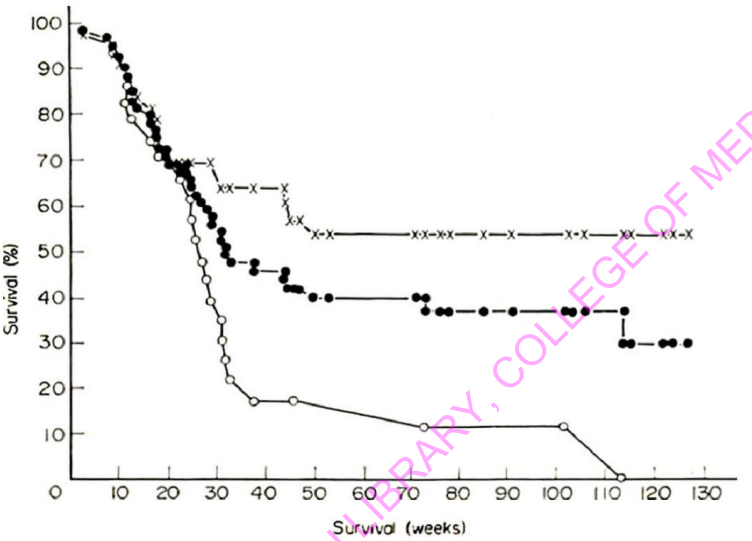

FIG. 1. Survival curves of BL patients with and without CNS involvement (actuarially calculated). ×—×, All treated patients excluding those presenting or developing CNS involvement (forty-three patients); ●—●, all treated patients (sixty-seven patients); ○—○, patients presenting with or developing CNS involvement (twenty-four patients).

course of all patients who presented with or developed CNS involvement was a rapidly downhill one. Progressive general debility and wasting featured prominently in the terminal stages. Of the twenty-two patients presenting with or developing CNS abnormalities and who received intrathecal therapy, only two are presently alive and tumour-free 102 and 20 weeks after onset of neurological symptoms. One patient survived for 46 weeks as of cut-off date for observation, but has since died.

Figure 1 shows the actuarially calculated survival curves of (i) treated BL patients without CNS involvement (forty-three), (ii) all treated patients with BL (sixty-seven), and (iii) twenty-four treated patients who had CNS involvement (presenting and developing). The extremely poor prognosis of the last group is obvious from the comparison of the three survival curves.

CONCLUSIONS

The following conclusions can be surmized from analysis of our present series:

(1) Involvement of the central nervous system in Burkitt's lymphoma seems to occur

relatively frequently. In our series, twenty-five out of seventy-five patients (33%) showed clinical and/or cytological evidence of CNS involvement. This closely parallels findings reported from Nairobi, Ibadan and Kampala (Frank, 1968; Odeku & Osuntokun, 1968; Ziegler *et al.*, 1970). The most frequent neurological manifestations indicating CNS involvement, apart from paraplegia, are cranial neuropathies, root/peripheral neuropathies, headaches and altered consciousness.

(2) Meningeal involvement (malignant pleocytosis) is present in almost all BL patients with neurological abnormalities and may even be present in the absence of neurological symptoms. The diagnosis of CNS involvement and proper staging of such patients depend solely on the cytological examination of the CSF for malignant cells, on admission and at frequent intervals thereafter.

(3) Burkitt's lymphoma patients may either present with CNS involvement when first seen, or CNS involvement may develop during the course of the disease. Patients who develop CNS involvement may do so while receiving chemotherapy, while in complete remission, or with relapse. The development of neurological manifestations is thus completely unpredictable and can occur any time. There was no correlation between staging on admission and subsequent development of CNS involvement in our series. Stage III patients (abdominal/retroperitoneal tumours) seem to run a higher risk of developing CNS involvement than stage I–II patients (facial tumours), but the difference is not statistically significant in our present series.

(4) Patients with CNS involvement (presenting or developing) have generally a poor prognosis. They constitute presently a great therapeutic challenge for physicians in care of patients with Burkitt's lymphoma.

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