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Tropical Splenomegaly Syndrome in Zambia: Further Observations and Effects of Cycloguanil and Proguanil

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Summary

Nineteen Zambian patients with the tropical splenomegaly syndrome and sinusoidal lymphocytosis on liver biopsy were studied. The association of macrobulinaemia with the tropical splenomegaly syndrome has again been confirmed. Sixteen patients were treated with antimalarials—12 with cycloguanil pamoate alone, 3 with cycloguanil and proguanil, and 1 with proguanil alone. Twelve patients were observed for periods of sufficient length for the drug effect to be assessed, and in 11 there was a good response in terms of decrease in spleen size.

Cycloguanil pamoate may be of value both for prophylaxis and treatment in areas where tropical splenomegaly syndrome is endemic.

Introduction

The tropical splenomegaly syndrome has been the subject of several reviews during the past two years (Pitney, 1968; *British Medical Journal*, 1967, 1969). Previous studies in Zambia showed that tropical splenomegaly syndrome occurring there was similar to that described in other parts of Africa (Lowenthal et al., 1966) and also that long-term antimalarial prophylaxis with proguanil was beneficial (Lowenthal and Hutt, 1968). Similar results, with more complete remissions, have been found in two larger series of cases treated with proguanil in Nigeria (Watson-Williams and Allan, 1968; Sagoe, 1970). A double-blind trial on cases of tropical splenomegaly syndrome in Uganda with long-term chloroquine therapy has also shown significant improvement in patients' symptoms and spleen size (Stuiver et al., 1971). Earlier experience with long-term treatment with proguanil

showed that it was not always easy to ensure that the drug was continually taken over a long period of time. For this reason it was decided to treat cases of tropical splenomegaly syndrome with the depot injectable antimalarial cycloguanil pamoate (Camolar) either alone or in some cases combined with proguanil.

Patients and Methods

Nineteen patients (13 male and 6 female) who fulfilled the diagnostic criteria for tropical splenomegaly syndrome (Marsden and Hamilton, 1969) were admitted to the wards of the Ndola Central Hospital during the period December 1968 to March 1970. In all cases a detailed clinical history and physical examination were carried out. Spleen size was measured along the longest palpable axis of the organ. All clinical examinations were made by one of us (M.N.L.). Laboratory examinations included: haemoglobin, white count and differential, thick blood film for malarial parasites, urine analysis and stool examination for parasites in all cases, haemoglobin electrophoresis in 14 patients, and sternal marrow puncture in 12 patients. Percutaneous liver biopsy was performed in all 19 patients and the diagnosis of tropical splenomegaly syndrome with hepatic sinusoidal lymphocytosis was established according to previous criteria (Marsden et al., 1967). Repeat liver biopsies were done in five patients at intervals after treatment had started. Other investigations, including plasma protein levels, empirical liver function tests, agglutinations against brucella and salmonella organisms, serum iron levels, and chest x-ray examination, were done in most cases.

Immunological Studies.—IgM levels were measured in 17 cases by a modification of the method of Mancini et al. (1965). The assay was repeated in seven cases after therapy, and in three of these a third estimation was made after a further interval. For the purpose of providing control values IgM was assayed in two other groups of patients. The first included patients with moderate to massive splenomegaly due to chronic myeloid leukaemia (3 cases), primary myeloid metaplasia (2), schistosomiasis (5), tropical splenomegaly syndrome without hepatic sinusoidal lymphocytosis (4), hepatic cirrhosis (6), and one case each of tuberculosis, amyloidosis, and con-

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genital hepatic fibrosis; the second group comprised seven patients without splenomegaly who were admitted with trauma or eye diseases.

Treatment

Antimalarial.—Thirteen patients were given a short initial course of chloroquine of up to 1.5 g total over two to three days. Previous experience in Zambia and Uganda had shown that this would not affect spleen size. In the assessment of long-term antimalarial therapy 12 patients were given cycloguanil only, three received both cycloguanil and proguanil, and one case was given proguanil only. Details of the proguanil and cycloguanil regimens are shown in Tables II and III. Three patients (Cases 15, 17, and 18) were not treated with either drug and are briefly included in this paper in regard to their clinical and immunological findings. Cases

5, 6, and 14 received large doses of cycloguanil at a single administration, 3 ml into each buttock. No complications attended the use of cycloguanil in this series or the employment of these unusually large doses of proguanil.

Other Therapy.—The complex clinical situation in many of these patients required the administration of a variety of other drugs. One patient (Case 1) was eventually given a short course of chlorambucil (28 mg total) and prednisolone (140 mg total). She was also given oral iron, folic acid, and vitamin B₁₂. Two patients (Cases 2 and 6) received iron-dextran by total dose infusion. None of the other drugs used are likely to have affected the size of the spleen or the blood picture.

Results

The initial clinical and laboratory findings are given in Table I and are essentially similar to those previously reported. The

TABLE I—Clinical and Laboratory Data on 19 Patients with Tropical Splenomegaly Syndrome

Case No.	Age	Sex	Spleen† (cm)	IgM	Hb Electr.	Liver Biopsy			Liver (cm)	Comments
						H.S.L.	Portal Lymphocytes	Portal Fibrosis		
1	45	F	17	640	AA	3	0	0	5	Hookworm. Cardiac failure. Strongyloides
2	16	M	10	156	AA	2	0	0	5	Hookworm. Tuberculosis
3	*50	F	16	600	AS	2	3	0	4	
4	57	M	20‡	2,160	AS	2	2	0	7.5	Mitral incompetence. Cardiac failure
5	*60	M	14	360	AA	1	0	0	5	
6	*50	F	20	232	AA	3	2	1	10	Hookworm. Pyelonephritis
7	29	F	11	720	AA	1	0	0	4	Abortion. Hookworm
8	*30	F	20‡	960	AA	3	1	0	6	
9	*55	M	10	1,480	—	2	1	1	5	Schistosomiasis
10	59	M	20	—	AA	1	1	0	2	Haematemesis. Leg ulcer
11	*25	M	17	1,100	AA	2	0	0	4	Pyelonephritis
12	16	M	10	570	AA	1	1	0	0	Hookworm. Malnutrition
13	*50	M	10	1,880	AA	2	0	0	5	
14	44	M	10	1,520	AA	2	0	0	6	Strongyloides
15	*40	M	12	1,200	—	1	0	0	1	Polyarthritis
16	*60	F	6	1,440	—	1	0	0	0	
17	13	M	7	720	—	1	0	2	8	Endomyocardial fibrosis
18	18	F	11	400	AA	2	1	0	7	Nephrotic syndrome
19	*50	M	12	—	—	1	0	0	8	Chronic lung disease

*Approximate.

†See text for measurement.

‡Right iliac fossa.

H.S.L. = Hepatic sinusoidal lymphocytosis.

TABLE II—Effect of Cycloguanil Pamoate (C.P.) on Spleen Size in 12 Patients

Case No.	Spleen before C.P. (cm)	Spleen after C.P. (cm)	% Reduction	Cycloguanil Pamoate					Comment
				No. of Injections	Total Dose (mg)	Days between Injections	Days between First Inj. and Final Exam.	Days between Last Inj. and Final Exam.	
1	17	0→8	53	5	1,470	107, 214, 96, 113	529	27	Initial response with relapse (See also text)
2	10	2	80	3	1,050	155, 279	458	24	Good response
5	14	14		1	840		22	22	Follow-up too short
6	20	13	35	1	840		90	90	Response
7	11	50	55	3	1,050	87, 105	283	191	Good response
8	20*	11	45	2	700	70	160	90	Good response
9	10	10		1	350		37	37	Follow-up too short
10	20	20		2	700	103	133	30	No response
11	17	8	53	2	700	132	181	49	Good response
14	10	0	100	1	840		344	344	Good response
16	6	5.5		1	210		30	30	Follow-up too short
19	12	1	75	1	350		89	89	Good response

*Right iliac fossa.

TABLE III—Effect of Cycloguanil Pamoate and/or Proguanil on Spleen Size in Four Patients

Case No.	Spleen before (cm)	Spleen after (cm)	% Reduction	No. of Injections	Cycloguanil Pamoate				Proguanil			Comment
					Total Dose (mg)	Days between Injections	Days between First Inj. and Final Exam.	Days between Last Inj. and Final Exam.	No. of Days Given	Daily Dose (mg)	Total Dose (mg)	
3	16	8	50	3	840	119, 183	384	146	56	300	16,800	Good response
4	20	14	30	4	1,190	92, 91, 107	533	243	101	200	20,210	Response
12	10	10		1	210				19	100	1,900	Follow-up too short
13	10	6	40						34	400	13,600	Response

IgM levels in 17 cases of tropical splenomegaly syndrome with hepatic sinusoidal lymphocytosis before treatment ranged from 156 to 2,160 mg/100 ml, with a mean of 949 mg/100 ml. This was significantly higher than the mean of 384 mg/100 ml in the 23 cases with splenomegaly of diverse cause, or the mean of 198 mg/100 ml in the seven patients without splenomegaly. The range and mean of these results may be compared with the normal adult Nigerian range and mean (50-400, mean 189 mg/100 ml), and the range and mean from Nigerians with tropical splenomegaly syndrome who respond to antimalarial therapy (860-3,000, mean 1,799 mg/100 ml) and Nigerians with tropical splenomegaly syndrome who do not respond to antimalarial therapy (20-325, mean 81 mg/100 ml) (Sagoe, 1970).

From Table I it is apparent that most patients had other diseases in addition to tropical splenomegaly syndrome. While some of these may have contributed to the anaemia, there is no evidence that they were the cause of the splenomegaly. The presence of multiple morbidity is similar to our previous experience with Zambian patients. Cases 3 and 4 were found to be carriers of the sickle-cell trait. These were two of the oldest patients in the group and were the only ones to have appreciable adenopathy. Lymph node biopsy in Case 4 showed some lymphocytic proliferation, but not of a degree to suggest lymphoma.

EFFECT OF TREATMENT

In the group of 12 cases treated with cycloguanil (Table II) three were under observation for only three to five weeks; none of these showed any change in spleen size. Previous experience indicated that treatment often has to be continued for at least three months before any appreciable effect is noticed. One patient (Case 10) who was observed for 113 days showed no significant reduction in spleen size, and is classified as a non-responder. One other patient who showed no response after 192 days had considerable diminution in splenic size when seen after 283 days. There were therefore eight patients who showed a significant reduction in spleen size over periods ranging from 64 to 529 days, though in one patient this was temporary. This patient (Case 1) had a severe haemolytic anaemia and gross splenomegaly when first seen. After the administration of cycloguanil the spleen shrank and was impalpable after 82 days and the anaemia improved. Six months later, however, she was readmitted with increasing anaemia and jaundice. The spleen now measured 14 cm, the cervical and axillary nodes were enlarged, and the haemolysis had returned—haemoglobin 7 g/100 ml and reticulocytes 25%. Further injections of cycloguanil and the administration of proguanil had no effect. She was then given cyclophosphamide 250 mg daily for 17 days. This resulted in a rise in haemoglobin, a decrease in reticulocytes, and a reduction in spleen size.

While this case fulfilled all the criteria for tropical splenomegaly syndrome, the presence of an overt haemolytic anaemia and the recrudescence of splenomegaly after an initial response are unusual. These features suggest that the patient may have developed a malignant lymphoreticular disease.

Two of the three cases treated with cycloguanil and proguanil showed pronounced reduction in spleen size; one case was not observed for sufficient time to assess the effect of treatment (Table III). One case treated with proguanil alone had an appreciable reduction in spleen size after 34 days. Five of those who responded to treatment had a second liver biopsy. In four of these there was a definite reduction in hepatic sinusoidal lymphocytosis after periods ranging from 90 to 408 days. There was no change in the appearance in the fifth case but the time interval from the start of treatment was only 48 days.

Discussion

The initial clinical and laboratory findings in these cases are typical of tropical splenomegaly syndrome with hepatic sinusoidal lymphocytosis, though the finding of two cases with haemoglobin AS on electrophoresis is unusual. Hamilton *et al.* (1969) found Hb AA exclusively in 143 patients with tropical splenomegaly syndrome in Uganda. The rate of 14% in the 14 patients tested in this series compares with rates varying from 13.5 to 19.7% in representatives from the same tribal groups and districts in Zambia (Barclay *et al.*, 1970); the significance of this requires a much larger study.

The effects of cycloguanil in nine patients observed for periods of from 64 to 529 days were, in the main, successful in reducing spleen size, and only one case failed to show any improvement. Earlier experience with long-term proguanil, however, suggests that therapy and observation should be continued for at least a year before one can classify cases as totally unresponsive. The relapse in Case 1 also suggests that splenomegaly may be influenced by other factors, such as an overt haemolytic anaemia, or alternatively, as Sagoe (1970) has implied, that unresponsiveness may indicate a lymphomatous transformation. In her series of cases recently reported from Nigeria, Sagoe showed that response to prolonged proguanil therapy was only found in cases of tropical splenomegaly syndrome with high IgM levels and with normal phytohaemagglutinin (PHA)-induced lymphocyte transformation. Non-responders, by contrast, had lower IgM levels and their lymphocytes failed to transform with PHA; some of the latter had clear-cut evidence of lymphomatous transformation.

In a recent double-blind therapeutic trial reported from Uganda it was shown that patients with tropical splenomegaly syndrome and hepatic sinusoidal lymphocytosis all responded well to long-term therapy with an initial course of primaquine followed by chloroquine. The possibility that both proguanil and chloroquine are acting as cytotoxic rather than antimalarial agents is discussed by Sagoe (1970) and by Stuiver *et al.* (1971); the overall evidence suggests that the latter mode of action is most likely to account for their therapeutic effect. The clear-cut distinction between responders and non-responders (Sagoe, 1970) is only partly borne out by the findings in this series. Of the 10 patients who showed a response to treatment, seven had IgM levels over 500 mg/100 ml and two fell within the normal range for rural Africans. Four out of the five patients who had a second liver biopsy (all responders) showed a decrease in hepatic sinusoidal lymphocytosis. In the Nigerian series selection for inclusion in the trial did not include hepatic sinusoidal lymphocytosis on liver biopsy, though this was present more often in responders than in non-responders.

The results reported here and from Nigeria and Uganda indicate that prolonged antimalarial therapy is the treatment of choice in tropical splenomegaly syndrome. Our findings suggest that cycloguanil might be of value where facilities for attending follow-up clinics are poor, or where there is difficulty in ensuring that pills are taken, both situations not uncommon in rural areas where tropical splenomegaly syndrome is seen. Further studies using a variety of measurements, such as IgM levels and PHA transformation, are necessary in various geographical areas to determine whether responsiveness can always be predicted, to elucidate the relation between cases of tropical splenomegaly syndrome with and without hepatic sinusoidal lymphocytosis, and to evaluate the frequency of true neoplastic lymphoid proliferation.

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Myocardial Infarction and Deep-vein Thrombosis

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Summary

In a study of 52 patients admitted into the coronary intensive care unit the incidence of deep-vein thrombosis was measured with the ¹²⁵I-fibrinogen test. Of these patients 31 were eventually confirmed to be suffering from acute myocardial infarction. This preliminary study showed that in patients with a confirmed infarct who were not treated with anticoagulants the incidence of deep-vein thrombosis was 38% and in those treated it was 5.5%. In patients who were "severely ill" from whatever the cause there was a high incidence of deep-vein thrombosis (68%).

Introduction

The true incidence of deep-vein thrombosis cannot be estimated clinically because signs are unreliable in diagnosing the condition (Flanc *et al.*, 1968; Negus *et al.*, 1968). The ¹²⁵I-fibrinogen test, however, is an accurate method of detecting thrombosis at the earliest stage (Atkins and Hawkins, 1965; Flanc *et al.*, 1968; Negus *et al.*, 1968). By using a ratemeter (Kakkar *et al.*, 1970b) the technique is rapid and simple and can be used as a routine screening procedure in a large number of patients. This technique was adopted in the present study.

In the recent M.R.C. report (1969) post-mortem studies revealed pulmonary embolism in 8.3% of patients with acute myocardial infarction who died. In a study of 240 consecutive post-mortem reports of patients with acute myocardial infarction at King's College Hospital it was found that

19 (7.9%) had macroscopic pulmonary emboli causing or contributing to their death (Nicolaidis, 1970). Similar results have been obtained by others (Browder *et al.*, 1959; Hilden *et al.*, 1961; Kucera, 1966). The present study was prompted by the above findings, which suggested a high incidence of deep-vein thrombosis in association with myocardial infarction. There is no doubt that effective attempts to treat deep-vein thrombosis and prevent pulmonary embolism are more successful when carried out at an early stage (Kakkar *et al.*, 1969).

Patients and Methods

Fifty-two patients admitted to the coronary intensive care unit were studied. All had been admitted as emergencies with acute chest pain and were well previous to this. Patients aged under 40 and those who had a history or clinical signs of deep-vein thrombosis were excluded. The diagnosis of myocardial infarction was subsequently confirmed in 31 patients according to electrocardiographic and enzymatic (serum aspartate aminotransferase and lactate dehydrogenase) evidence. Eighteen of the patients with a confirmed infarct were treated with anticoagulants. This was part of the routine management practised by some of the physicians under whose care the patients were admitted. In these a continuous intravenous infusion of heparin (10,000 units six-hourly for 36 hours) and oral anticoagulants were started immediately on admission if the infarct was obvious or as soon as it was confirmed, usually within 24 to 48 hours. Subsequently the dose of oral anticoagulants was regulated to maintain the prothrombin time between one and a half and two times the control value. The remaining 13 patients with confirmed infarcts were not treated with anticoagulants (Table I). Apart from anticoagulation both groups received identical treatment.

DIAGNOSIS OF DEEP-VEIN THROMBOSIS

All the patients were screened by the ¹²⁵I-fibrinogen test, using the Pitman 235 isotope localization monitor (Kakkar *et al.*, 1970b). The principle of this test is that ¹²⁵I-fibrinogen injected into the circulation is incorporated into a forming thrombus, and this is detected by the increased radioactivity at that site.

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