INCREASED PLASMA IRON AND LIVER PATHOLOGY IN AFRICANS WITH PORPHYRIA

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We recently drew attention to a grey-black pigmentation of the face in Africans (Bantu) shown by us to have marked hepatic siderosis.[1] We have also noted a contrast between this uniform pigmentation and the 'blotchy' appearance of the skin in African patients with porphyria. This observation, and the fact that we had found a high incidence of liver pathology and disturbances in plasma iron in siderotic patients,[2,3] prompted us to perform liver biopsies and plasma-iron estimations in porphyric patients.

Material and Methods

One of us (N.M.L.) has seen 37 patients (20 female) with porphyria in the out-patient department of this hospital during the past 9 months, and many more have attended the dermatology clinic. Of these 37 patients it was possible to arrange admission of 13 males and 2 females for liver biopsy. Their ages ranged from 32 to 60 years (mean 43 years).

The urine of all 37 patients fluoresced in ultraviolet light,

TABLE I

Case No.	Sex	Age	Skin			Abdom. Colic	Neurol. Signs	Urine			Serum Bilirub. (mg.%)	Hb. (g.%)	Plasma Iron (µg.%)	TIBC (µg.%)	% Saturation
			Hyperpig.	Scars	Vesicles			PBG	Uro. I	Uro. III					
1	F	60	+	+	0	mild	+				<·8	14·3	106	215	49
2	M	52	+	+	+	mild	0				1·9	12·5	101	190	53
3	F	49	+	+	+	mild	+				<·8	16·4			
4	M	47	+	+	0	0	+				<·8	15·8			
5	M	33	+	+	+	0	+	0	+	0	<·8	16·2	300	449	67
6	M	38	+	+	0	0	+				1·4	16·2	346	325	100
7	M	37	+	+	+	0	0				1·1	15·6	255	245	100
8	M	42	+	+	0	0	0				<·8	16·2	208	200	100
9	M	33	+	+	0	mild	0	+	+	0	<·8	15·8	403	360	100
10	M	32	+	+	+	0	0	0	+	+	1·3	19·1	276	262	100
11	M	51	+	+	+	0	0	0	+	0	1·2	14·8			
12	M	48	+	0	0	mild	+	+	+	0	<·8	17·0	245	359	68
13	M	40	+	+	+	0	0	+	+	0	0·9	15·5	338	337	100
14	M	40	+	+	+	0	0	+	+	0	<·8	19·5	269	212	100
15	M	43	+	+	0	0	0	0	+	0	<·8	16·3	212	271	79

PBG = porphobilinogen. Uro. = uroporphyrin. TIBC = total iron-binding capacity.

and in 8 of them urinary porphyrins were differentiated spectroscopically. Plasma iron and total iron-binding capacity were estimated by the procedure previously described.[3] Liver biopsies were performed by the transabdominal route by means of the apparatus described by Gillman and Gillman.[4] Serial sections were stained for reticulin and iron; they were also stained with haematoxylin and eosin and by a modified Masson technique.

RESULTS

The clinical and laboratory findings are summarized in Table I.

Clinical Features

All our patients had the same broad clinical pattern as the African porphyric patients described by Barnes,[5] Gelfand and Mitchell,[6] and Shaper.[7] Of the 15 patients, 14 had typical depigmented 'scars' on the dorsa of their hands and other exposed areas. Active vesicles were present in 8 patients. One male (case 12) showed only excessive pigmentation, particularly of the face, which was of recent origin (2 years) and which was the patient's main complaint. In this hospital, hypertrichosis is more commonly found in females than in males with porphyria, and was absent in 6 of our male patients.

A history of *abdominal colic* was given by 5 patients, but in none was the pain severe. *Neurological signs* such as calf tenderness, hyperreflexia, absent reflexes, or impairment of sensation, were detected in 6 patients. Case 9 had been admitted to a mental institution during 1958 for a transient psychosis.

In all cases the liver was appreciably enlarged and of firm consistency. The spleen was palpable only in case 13. No patient presented with clinical features frankly suggestive of liver disease.

Laboratory Findings

In the 8 cases whose *urine* was examined spectroscopically, uroporphyrin I was present in all and was the predominant pigment in all except case 12, who showed no skin lesions, apart from the excessive pigmentation. Porphobilinogen was present in 4 cases, while uroporphyrin III was present in 1.

The *fasting blood sugar* was determined in cases 9, 13, 14 and 15, and was below 90 mg. per 100 ml. in all four.

The *haemoglobin* was normal or high in all patients, averaging 16·1 g. per 100 ml.

The *plasma iron* was above 200 μg. per 100 ml. in 10 of the 12 patients in whom it was determined. Both the remaining patients, whose plasma-iron levels were normal, were suffering from acute dysentery; infections are known to depress plasma-iron levels. The values for total iron-binding capacity were less consistent, being decreased in 5, relatively normal in 6, and elevated in 1. There was complete saturation of the total iron-binding capacity in 7 out of the 12 patients.

Liver Biopsy Findings

The biopsy specimens all showed evidence of liver damage, which varied from minor alterations in the intralobular and periportal reticulin framework (Fig. 1) to gross distortion of lobular architecture with scarring and hyperplastic nodules typical of cirrhosis (Figs. 2 and 3). Only 1 case showed the type of portal fibrosis usually found in African patients with advanced hepatic siderosis.[2] Iron-containing pigment was present in the liver in significant amounts in 12 patients, but its distribution was different from that usually found in siderotic patients in that hepatocellular iron was minimal and Kupffer-cell iron tended to predominate. In no patient was iron accumulation as heavy as that commonly found in our siderotic patients. Widespread fatty change of moderate degree was present in specimens from 9 patients.

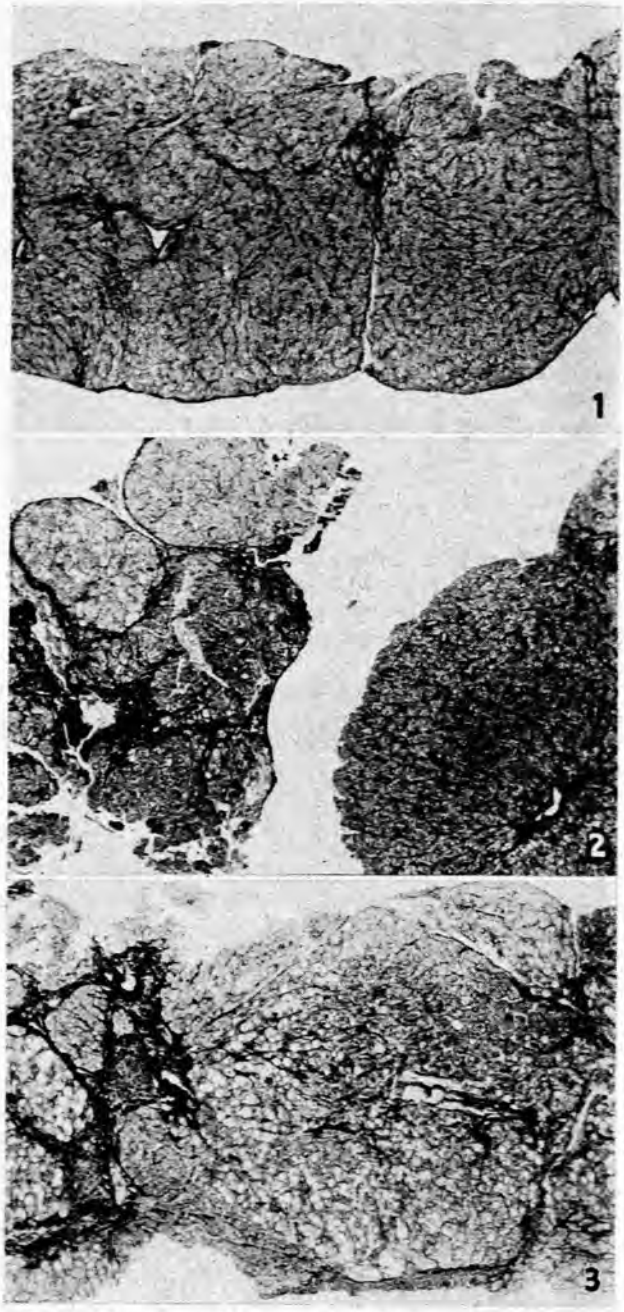

Fig. 1. Liver biopsy from case 7. Reticulin stain × 35.
Fig. 2. Liver biopsy from case 12. Reticulin stain × 35.
Fig. 3. Liver biopsy from case 11. Reticulin stain × 35.

DISCUSSION

The occurrence of marked elevations of plasma iron together with relatively normal total iron-binding capacity in our

patients is an unexpected finding. Marked increases in plasma iron levels have been shown in idiopathic haemochromatosis and transfusion siderosis,[8] in dietary siderosis in Africans,[9] and in acute hepatitis.[10] The association of high plasma-iron levels with somewhat reduced or relatively normal total iron-binding capacity results in a picture almost identical with that found in idiopathic haemochromatosis and transfusion siderosis, but different from that in African siderosis (Fig. 4). It would be of great interest to know whether similar disturbances in iron metabolism occur in other groups of porphyric patients, both in South Africa and elsewhere.

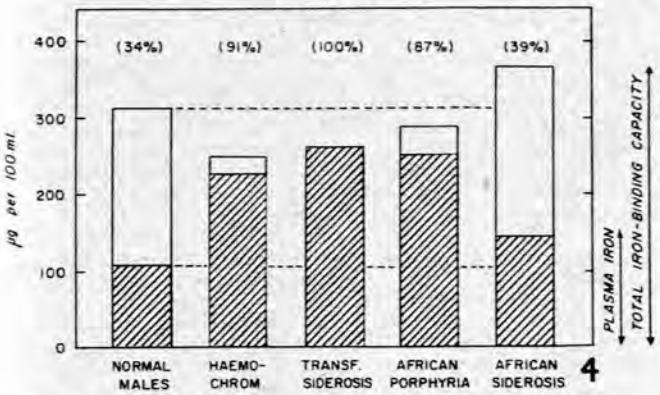

Fig. 4. Mean plasma iron and total iron-binding capacity in 12 Africans with porphyria (present study) contrasted with findings in normal males, cases with idiopathic haemochromatosis[8] and transfusion siderosis,[8] and Africans with advanced siderosis.[3] Figures in parenthesis denote percent saturation of total iron-binding capacity.

The famous case of Tio and his associates[11] provides evidence that erstwhile normal liver cells can acquire a disordered porphyrin metabolism, and Barnes[5] postulates that an acquired deviation of pigment synthesis may possibly account for porphyria in Africans. We were unable to elicit any history of cutaneous lesions in the families of our patients and Barnes's biochemical investigation of families of porphyric Africans was negative. He has shown that porphyria in Africans differs from the condition as described in White South Africans and in Europeans (particularly in Sweden), in that in Africans it is probably an acquired condition, involving a disturbance in porphyrin metabolism at an intermediate stage.

Our patients closely resemble the group described by Barnes in Union Africans and by Gelfand and Mitchell[6] in Rhodesia. Like the latter workers we have found that most of our patients consume alcoholic beverages rather freely. Barnes has shown that in his African patients the faecal excretion of porphyrins is either slightly increased or normal, as compared with his White South African porphyric patients. At the same time, the excretion of copro- and protoporphyrin in the urine of porphyric Africans is not increased, and the predominant pigment in the urine is uroporphyrin, which is usually excreted in exceptional amounts (as much as 2,000 μg. per 24 hours). Thus, porphyria in the African cannot be attributed primarily to faulty excretion by a damaged liver, but seems rather to be due to some defect in the intermediate stages of the biosynthesis of protoporphyrin.

The pattern of hepatic fibrosis in our porphyric Africans was different from that found in our siderotic Africans. Moreover, the different distribution of the iron in the liver suggests some disorder of iron metabolism in porphyria different from that in African siderosis.

The histological appearance of the liver in porphyric Africans has, to our knowledge, not previously been reported. Despite the absence of frank clinical liver disease, the presence in our patients of a distinct pattern of hepatic injury is probably not coincidental. Barnes[5] has presented evidence that porphyria in the African cannot be attributed to faulty porphyrin excretion by a damaged liver. The association, therefore, of frank liver pathology with elevated plasma-iron levels may well provide a clue to the specific underlying disorder responsible for the liver damage and the disturbances in both porphyrin and iron metabolism in our patients.

SUMMARY

Investigations have been made into 13 male and 2 female Africans with porphyria. Cutaneous lesions were present in all patients and in 8 of the patients whose urine was examined spectroscopically, the predominant pigment excreted in the urine was uroporphyrin I. These cases thus conformed both clinically and biochemically with the group of porphyric Africans described by Barnes.[5]

The plasma iron was above 200 μg. per 100 ml. in 10 of the 12 patients whose plasma iron was measured. There was complete saturation of the total iron-binding capacity in 7 cases. Haemoglobin levels were normal or high in all patients. Liver biopsies showed varying degrees of hepatic fibrosis in all cases.

The possible significance of these findings is discussed.

ADDENDUM

Since this paper was written an additional 31 Africans suffering from porphyria have been investigated. In all these 31 patients, the urine was found on spectroscopic examination to contain uroporphyrin I as the predominant pigment excreted. In addition apart from patients with overt infection (mainly tuberculosis) it was found that the plasma-iron levels were all above 200μg./100 ml. These subsequent cases will be described elsewhere.

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