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Increased Urinary Porphyrin Excretion in Sickle Cell Crises.* (31387)

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Urines voided during painful sickle cell crises show a characteristic dark brown coloration even though urinary secretion is voluminous and of low specific gravity(1). The depth of color is further intensified on standing and/or exposure to sunlight. On illumination with Wood's light one of the authors (H.N.N.) observed brilliant magenta fluorescence of sediments suggesting presence of adsorbed porphyrins which, subsequently, were confirmed by qualitative extraction methods (2). A quantitative study was then undertaken in order to determine ranges of urinary porphyrins and their precursors excreted during and after typical painful and febrile crises and in patients with sickle cell disease hospitalized for conditions other than painful crisis.

Materials and methods. Patients with sickle cell disease were made available for this study through the "Sickle Cell Center," Division of Hematology and the Clinical Research Center, University of Tennessee. The material consisted of 82 urine samples, 68 of which were 24-hour specimens and 14 random specimens collected from 18 patients with sickle cell disease including 8 during painful crises. Analytical methods employed were those developed by one of the authors (F.S.S.) and collaborators(3-7) using "Florisil" adsorption and elution of porphyrins and spectrophotometry between 380-430 mμ (Soret band) in a Beckman Model DU spectrophotometer. Adsorption and elution of porphobilinogen (PBG), o-aminolevulinic acid (ALA) and aminoacetone (AA) was performed by resin column chromatography(7) and spectrophotometry of the corresponding aldehyde compounds according to Mauzerall and Granick(8).

Results. The values obtained for total porphyrins, copro- and uroporphyrins, PBG, ALA, and AA, based on analyses of 24-hour urine specimens during painful sickle cell crises, during recovery phases, and during conditions other than painful crisis are sum-

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marized in Table I. It is noted that coproporphyrins were increased during crises in all of the patients examined; total porphyrins were increased in 89% and uroporphyrins in 61%. Excretion of total porphyrins ranged up to 2,344 μg/24 hr and up to 1.9 μg/ml in random samples, about a 10-fold increase as compared with upper normal limits. In some patients during crises the concentration of porphyrins was normal or low, but the usually large volumes of urine, mentioned above(1), yielded high daily excretion values.

The average values of total, uro- and coproporyhyrins during painful crises were approximately 3 to 4 times greater than during the recovery phases and non-crisis periods. By contrast, porphyrin concentrations during recovery phases or in patients not in painful crises were within the range of normal variation. The porphyrin precursors PBG, ALA

TABLE I. Urinary Porphyrins and Precursors in Relation to Crises in Sickle Cell Disease.

Substances determined	Clinical status	No. of: Patients	No. of: Crises, recovery phases	No. of: Specimens	Incidence of increase (%)	Porphyrins: Observed values,* μg/24 hr: Avg	Observed values,* μg/24 hr: Range	Normal values,* μg/24 hr: Upper normal limit	Normal values,* μg/24 hr: Range
Total porphyrin	Painful crisis	9	10	29	89	439	45–2344		
	Recovery phase	3	3	12	16	99	11– 219	180	10– 180
	Other	2		14	12	103	3– 208		
Uroporphyrin	Painful crisis	8	9	24	61	53	0– 169		
	Recovery phase	3	3	10	16	13	0– 50	18	1– 18
	Other	2		11	7	14	0– 107		
Coproporphyrin	Painful crisis	7	8	20	100	258	164– 696		
	Recovery phase	3	3	10	16	87	5– 184	160	5– 160
	Other	2		11	19	95	3– 141		
Porphobilinogen	Painful crisis	6	6	16	35	896	0–2292		
	Recovery phase	3	3	11	8	434	0–1357	1400	160–1400
	Other	2		9	38	710	0–1313		
δ-Aminolevulinic acid	Painful crisis	8	8	19	53	2700	356–5143		
	Recovery phase	3	3	11	0	1393	42–2351	2600	830–2600
	Other	2		8	50	2666	1000–4813		
Aminoacetone	Painful crisis	8	8	20	18	923	315–2100		
	Recovery phase	3	3	11	0	532	272– 996	1200	130–1200
	Other	1		7	0	865	338–1113		

* Recovery of total, uro-, and coproporphyrins was 86% ± 4.2 (S.D.), 97% ± 5.2 (S.D.), and 94% ± 4.4 (S.D.); for PBG, ALA, and AA 89.6 ± 5.0 (S.D.), 89.8 ± 6.0 (S.D.), and 94.4 ± 9.0 (S.D.) respectively.

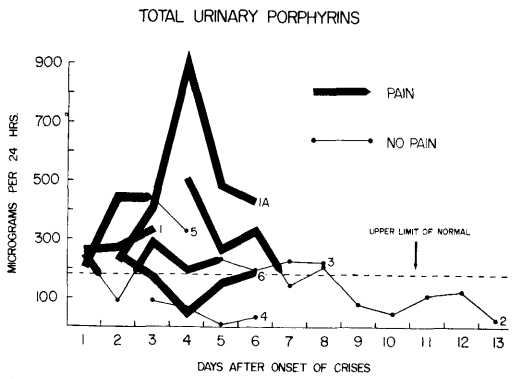

FIG. 1.

and AA were increased less frequently during crises than total, uro- and coproporphyrins, and average values were within normal range except those of ALA (Table I).

The total urinary porphyrin excretion values during 7 painful crises in 6 patients with sickle cell anemia who were observed 2 or more days are graphically presented in Fig. 1. Essential clinical information on these patients is summarized in Table II. In general it was noted that total porphyrin excretion was increased during early stages of the crises, tending to decrease as pain subsided and was normal in the steady state. Urine color depth during periods of recovery revealed progressive changes from dark-brown to light-amber. In Case 3, in which there was initial pain of knee joints followed by a pain-free interval and later by abdominal pain with possible splenic infarct, there was an initial dip in porphyrin excretion with subsequent greater elevation (Fig. 1). In Case 6, 4 of 5 values were within ranges of normal variation at time of pain and fever.

In one of our patients complaining of headache and soreness in chest and elbows, considered to be in painful crisis, total porphyrin values on 3 successive days were the highest observed in this series: 2344, 1555 and 1345 μg/24 hr. However, these values were not included in Fig. 1 since history and time of crisis onset were not reliable. Another patient, a 21-year-old female with Hgb SS and 6.9% fetal hemoglobin, presented right upper quadrant pain, liver tenderness, nausea and vomiting, with total serum bilirubin of 6.7 mg/100 ml, bilirubin glucuronide of 1.6 mg/100 ml and high urinary bilirubin. Underlying pathological changes were considered to be stasis of sickled cells in hepatic capillaries and secondary degenerative changes (hepatic crisis)(12). Total porphyrins, mainly coproporphyrins, were in the range of 300-400 μg/24 hr comparable to findings in other types of obstructive jaundice(9).

Porphyrins and precursors were determined on 2 patients with sickle cell disease who were not in crisis. One of these, a 19-year-old female with Hgb S-thalassemia, was observed before and following splenectomy. The total porphyrin values on 3 occasions previous to operation when patient had slight left upper quadrant discomfort from splenic infarction, and 3 values on days following operation were normal. Five days after splenectomy a total porphyrin excretion of 206 μg/24 hr, slightly

TABLE II. Clinical Data on 6 Patients in Sickle Cell Crises Presented in Fig. 1.

Case No.	Age, sex	Hemoglobin Gene type	Hemoglobin Fetal, %	Clinical features
1	17 ♂	SS	4.4	Severe chest pain; painful lymph node, right side of chest; fever.
1A*	"	"	"	Severe pain in legs and knees; fever; acidosis; muscle cramps.
2	16 ♀	SS	16.0	Chest pain and dyspnea; possible pulmonary infarct followed by 2 days of soreness.
3	12 ♀	SS	5.6	Severe pain in both knees followed by pain-free interval and later abdominal pain; splenic tenderness.
4	20 ♂	SS	7.2	Severe pain in chest and back followed by residual soreness.
5	33 ♂	SS	2.0	Pain in neck; abdominal distention followed by much residual soreness.
6	25 ♀	SS	6.2	Severe pain in abdomen and legs.

* Second crisis in Case No. 1.

above the normal limit, was obtained. The other patient, a 54-year-old male with Hgb SC disease and infected leg ulcer, showed 9 total porphyrin values from 4 to 149 μg/24 hr and only one value, 208 μg/24 hr above the normal limit of 180 μg/24 hr.

Discussion. Our findings reveal a rather consistent moderate, occasionally marked increase of urinary copro-, total, and uroporphyrins—in this order—and to a slight extent of porphyrin precursors ALA, PBG, and AA during painful and febrile sickle cell crises. Although the number of cases is small, it is our impression that total urinary porphyrin excretion generally parallels the severity of clinical symptomatology and is normal during recovery and the steady state.

Of considerable interest is the close resemblance of prominent clinical features in sickle cell crisis and acute porphyria, particularly evident in cases with episodes of excruciating abdominal pain which in both conditions has led to unnecessary laparotomies (9,10,11). Besides increase of urinary porphyrins there is evidence of vasoconstriction in both diseases(9,10,12,13).

Summary. Porphyrin excretion in urine was studied in 18 patients with sickle cell disease, including multiple observations in 6 patients during 7 typical painful and febrile crises. With few exceptions there was moderate to marked elevation of copro-, total, and uroporphyrins at time of pain and fever. Aminolevulinic acid, porphobilinogen, and aminoacetone during crises were within range of normal variation or only slightly increased. Following subsidence of pain and fever, total porphyrin values returned toward normal. Similarities between clinical features of painful sickle cell crisis and acute porphyria are pointed out.

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An Electron Microscopic Study of Lipoprotein Production and Release by the Isolated Perfused Rat Liver.* (31388)

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It has been well established that liver plays an active role in lipoprotein synthesis (1-5). If the theoretical dimensions of the high and low density lipoproteins calculated by Oncley(6) are correct, they should both be visible with the electron microscope. Nevertheless, this tool has been very little used

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