RENAL MANIFESTATIONS

IN CHILDREN WITH SICKLE CELL ANAEMIA

A Dissertation presented in part fulfilment for the Degree of Master of Medicine (Paediatrics) in the University of Nairobi.

By:

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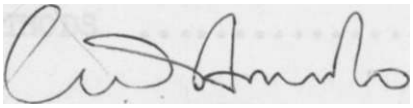
D E C L A R A T I O N

I certify that this thesis is my own original work and has not been presented for a Degree in any other University.



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Ihis Dissertation has been submitted for the examination with my approval as University Supervisor.

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(Prof. S.K. Ongeri)

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LIST OF ABBREVIATIONS.

S.C.A.	-	Sickle cell anaemia
S.C.D.	-	Sickle cell disease
P.H.P.F.	-	Per high power field
S.D.	-	Standard Deviation
G.F.R.	-	Glomerular filtration rate
$S_{\#}A$.	-	Surface area.

SUMMARY

Twenty one children admitted to the Kenyatta National Hospital with sickle cell anaemia were studied with the aim of detecting the renal defects associated with this haemoglobinopathy.

In a controlled study Investigation was limited to simple, non-invasive techniques which included urine analysis and culture, determination of creatinine clearance and urine flow rate, and a urine concentration test.

Patients in sickle cell crisis were shown to have a reduced GFR and urine flow rate. A urine concentration impairment which has been shown in other studies was confirmed. Further study on py^Lonephritis in sickle cell disease was recommended.

I N T R O D U C T I O N

Sickle cell anaemia was first described as a distinct disease entity by Herrick in 1910 (1). Following that discovery many other manifestations of the disorder involving such other organs and systems as the cardiovascular, the pulmonary, the kidneys and the eyes have been described (2). A large amount of work has gone into attempting to delineate the clinical features and the pathophysiology of this disorder in order to enable the development of suitable and rational management of sickle cell disease.

The World Health Organization in 1966 (3) estimated that sickle cell disease affected about 1% of all children born in tropical Africa, and that it was responsible for approximately 80,000 infant deaths annually in the same region. It seems that even today sickle cell disease in tropical Africa is a major childhood problem.

Sickle cell disease is a common disorder in parts of Kenya, with prevalence rates for the trait running up to 30% in certain communities (4). It is an important cause of morbidity. Mwangemi in 1977 (5) studying causes of morbidity and mortality among sicklers aged 13-33 years at the Kenyatta National Hospital Nairobi, confirmed skeletal and cardiovascular complications as being prominent whereas an earlier study by N^ai, Bwibo and Ogada (6) emphasized the importance of the haematological problems among children with sickle cell anaemia. No noteworthy renal manifestations were recorded in either of these studies.

She renal manifestations of sickle cell anaemia have been summarized by Bebrman (7) as comprising gross haematuria, papillary necrosis, the nephrotic syndrome, renal infarction, urinary concentrating defect and pyelonephritis. Ihese features have been confirmed and documented by other **M** studies (8,9,10,11,12).

There have been no studies on the renal involvement in sickle cell disease in Kenya. Ihis interested the author in view of the high prevalence of sickle cell disease in this region. Sickle cell nephropathy as reported elsewhere presents dramma-tically with haematuria. As was noted by the World Health Organization study group on haemaglobinopathies (3) early mortality appeared to be the rule in East and Central Africa. Longer survival was observed in West Africa and the West Indies while survival into adulthood was common in the United States of America. *The* reason for the apparent regional variability in severity of S.C.D. was not clear.

It is probable that early deaths among sicklers in our region preclude the development of obvious renal diseases

AIM

To study the renal manifestations of sickle cell anaemia in children admitted to the Kenyatta National Hospital.

MATERIALS AND METHODS

PATIENTS:

This study was conducted during the period July, 1980 to January, 1981. All patients destined for admission to the paediatric wards of the K.N.H. are initially admitted to the paediatric observation ward, a unit in the outpatient department.

Patients included in this study were admitted from the observation Ward by the author when and if bedspace was available, Ihey were otherwise unselected and the only criteria for inclusion into the study were:

(i) A diagnosis of sickle cell anaemia (HBSS) based on haemoglobin electrophoresis.

(ii) Absence of current or known recent antibiotic therapy, in view of the investigation for urinary tract infection.

CONTROLS

Due to ethical and other consideration it was not possible to admit normal children into the hospital for investigation. Therefore children admitted into the hospital were used as controls if they satisfied the following criteria:

(i) They had normal haemoglobin (HBAA) by haemoglobin electrophoresis.

(ii) They had no history or clinical features suggestive of renal disease.

(iii) Absence of current or known recent antibiotic therapy.

(iv) They were in good general physical status and were ambulatory.

The following procedures and investigations were performed on all patients and controls.

History and general physical examination which included age, sex,weight and height. Weight was taken with the subject standing on a spring balance.

Height was taken with the subject standing against a wall* Those too young to follow instruction had their length taken in the recumbent position.

A clean early morning voided midstream sample of urine was obtained. Immediately the following tests were performed.

(a) Observation of appearance
(b) A dipstick analysis for proteins, sugar and blood, using "N-^ultistix - Ames".
(c) Microscopic examination of urine sediment for cells and casts.
(d) Culture. The initial plating was done using a standard wire loop delivering a volume of 0.01 ml on to a plate containing Citrate-Lactose-Electrolyte-Deficient medium.

The medium was then incubated at 37C.for 24 hours before colony counts were done. Baterial growth was regarded as significant if there was a pure culture colony count of more than 10^ per millilitre.
For the estimation of urine volume and flow rate, a 24 hour urine sample was collected while the patient was on a free fluid intake regime. This period was from 8 a.m, to 8 a.9 of the next day. None of the patients was 6n intravenous fluids.

At the end of the collection period, 5 ml. of venous blood was obtained, centrifuged and the serum was preserved. The serum and the 24 hour urine samples were used to determine serum osmolality, serum creat-inine and urine creatinine concentration.

Serum osmolality was measured by a method utilizing freezing-point depression in a ^SiaueJ osmeter. These detenninations were performed at the department of Medical Physiology J-aboratories, University of Nairobi.

Creatinine determination was by a method utilizing Jaffe's Reaction (13) of serum protein precipitation. Colorimetry was done at 500nm. in a Unicam electronic spectrophotometer. This was done at the Department of Paediatrics Laboratory.

Urine flow rate was calculated using the formula:

Q • Urine flow rate, where:(.F.n.)
T"

Q • Urine volume (Ml)

T • Period of collection (Min)

Endogenous creatinine clearance was calculated using the formula: UV » Clearance, where
F

U - Urine Creatinine concentration

V - Volume of urine delivered per minute.

P - Plasma creatinine concentration.

A urine sample for the measurement of urine concentration was collected in the following way:

A twelve hour fluid starvation period was imposed, starting at 9 p.m. and ending at 9 a.m. the next day. This was supervised either by the subject's parent if one was available during that period, or by the nursing staff.

At the end of the twelve hours patients were asked to void urine. Hie first sample was discarded. Hie next sample of urine voided was used for the measurement of urine osmolality.

Ihe urine osmolality was measured as has been described for serum osmolality. Patients who were considered too ill had this test deferred until after there was general clinical improvement.

RESULTS:

(a) 21 patients with sickle cell anaemia were studied. Their ages and anthropometric data are presented in table I. There were 11 males and 10 females. Their ages ranged from 1.3 years to 11 years with a mean of 5.6 years. All these patients were admitted due to painful (vaso—occlusive) crisis.

TABLE I

rTHROPO METRIC DATA IN PATIENTS

Of ^M^OBI

WTTH SICKLE CELL ANAEMIA

N - 21

patient	AGE (YR)	SEX	WEIGHT (kg)	HEIGHT (CM)	SURFACE AREA (m^2)
S_1(O.J.$_1$)	5	M	21	110	0.8
S_2(K.O.)	1.6	M	11.5	80	0.51
S_3(H.O)	2	M	13	82	0.56
S4(B.W.)	1.3	F	8	70	0.41
s_5(o.o)	10	M	30	132	1.1
S6(V.R)	4.5	F	19	110	0.76
S7 (M.O.$_1$)	7	F	19	124	0.8
S8(G.O.I)	5	F	15.5	115	0.7
s^(o.J.$_2$)	5	M	18	107	0.74
^{S}10(A$_o$0.)	10	M	25	135	0.94
S11(O.R.)	11	F	32	144	1.1
S_{12}(B.A.)	5	F	17	105	0.71
S_{13}(G.0.2)	8	M	27	132	0.98
$^{S}I_4$(G.A)	2.5	F	10	90	0.5
S_{15}(C.A)	3	F	15	88	0.6
^{S}16<^{P}-^{0}-)	8	M	30	133	1.1
$^{s}i_7$(k.R.)	4	F	11.5	93	0.54
^{s} i e < W ;	4.5	M	14	97	0.62
	4	M	11.5	93	0.54
^{S}20(M.M.)	10	M	32	134	1.1
	6	F	15	109	0.66

(b) 13 controls were studied. There were 5 males and 8 females. Their ages ranged from 3$ years to 11 years, with a mean of 6.2 years© This data together with their diagnoses are presented in table 11$_0$

TABLE II

ANTHROPOMETRIC DATA IN CONTROLS.

N - 13

PATIENT	AGE (YR)	SEX	WEGIHT QCA)	HEIGHT (c~0	SURFACE AREA On*)	DIAGNOSIS
C^CL.K.)	10	F	21.5	135	0.88	HYPERTHYROIDISM
C5(M.K.)	8	F	22.5.	123	0.88	IRON DEFICIENCY ANAEMIA
C6(M.M.)	7	F	26.5	127	0.96	PITYRIASIS RUBRA PYLARIS
C7(E«W.)	10	F	21.5	110	0.82	PITYRIASIS RUBRA PYLARIS.
C8(L.A«)	3.5.	F	15	103	0.66	PO FALCIPARUM HALARIA
C_{10}(B.M.)	8	F	17	121	0.78	IRON DEFICIENCY ANAEMIA
C^CG.N.)	5	M	17	10**	0.7.	PRIMARY EPILEPSY
C_{12}(D.N.)	3*7	M	15*5	102	0.68	PRIMARY EPILEPSY
^{c}13CJ.W.)	11	F	26	1^2	0.98	HYDATID DISEASE
1^(K.L.)	6	M	20	118	0.8	HYDATID DISEASE
$^{c}1_5$(T.A.)	5	F	18	110	OO 7^	GASTROENTERITIS
C16(T.M.)	3	M	16	98	0.66	. HYPERACTIVITY
CI$_7$(P.N.)	5	M	19	112	0.78	P.FALCIPARUM MALARIA.

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The results of urine analyses performed on 7 sicklers and 2 controls are shown in table III and table IV respectively. The rest 6f the subjects had normal results.

TABLE III

URINE ANALYSIS IN

PATIENTS WITH SICKLE CELL ANAEMIA.

N-21

PATIENT	PROTIENS	SUGAR	RBC	WBC	CASTS	CULTURE.
				25 PHPF		KLEBSIELLA
				HPF		E.COLI
S5	TRACE				GRANULAR	
S7				5 PHPF		
Hz			MANY			
S18	• it		MANY			
S20			FEW			

TABLE IV

URINE ANALYSIS IN

CONTROLS

M » 13

PATIENT	PROTEINS	SUGAR	RBC	WBC	CASTS	CULTURE,
C7	TRACE			15PHPF		
	TRACE					

COMMENTS:

(a) Patients S13 (G.O,) and S18 (J.W} had macroscopic haematuria, Their haemoglobin levels were within the expected range J 6, 5* g/dl and 9.2 g/dl respectively. They received no blood transfusion during this admission. In both cases haematuria resolved and urine appeared normal within one we^k,

(b) Two patients S4- (BM) and S3 (H.OO had significant cultures of E, coli and Klebsiella organisms respectively,

(c) None of the controls had significant bacteriuria

(d) It is noted that controls C8 (L. A,) and C17 (P.N.) who were admitted due to P, Falciparum malaria infections did not have proteinuria or other urin$_a$r abnormalities,

URINE VOLUME. FLOWRATE AND SERUM OSMOLALITY

(a) The 24 hour urine volumes and the calculated urine flow rates are shown in table V for the sicklers.

TABLE V

2k **HOUR URINE VOLUME$_T$ URINE FLOW** RATE AND **SERUM OSMOLALITY** IN **PATIENTS** WITH **SICKLE CELL ANAEMIA**.

N = 21

24 HR URINE VOL. (ml.)	URINE FLOW RATE (ml/min./l.73nr	SERUM OSMOLALITY (mOsm/kg.)
4oo	0.6	295
330	0.78	300
350	1.75	290
560	1.64	288
1500	0.64	300
275	0.43	302
550	o.83	298
1200	2.06	305
960	1,56	310
.1460	1.87	280
1120	1.22	295
720	1.21	287
1000	1.23	296
580	1.40	288
350	0.70	301
850	0.93	306
800	1.78	286
^50	o.87	267
650	1.42	260
850	0.84	270
460		280
	1.18+ 0.51	290+ 23

urine flow rate ranged from 0.43 to 2.06 ml/min/1.73m^2 surface area a mean of 1.18+ 0.51 (1 S.D.).

(b) Pn controls had higher urine flow rates than the sicklers, ranging fr°**M** 1.02 to X. J& ^i**^STO** (table **VI).**

rnjLE VI.

9i4. HOUR URINE VOLUME URINE. F^OW RATE AND ^ggUH OSMOLALITY$_{j}$J$_{N}$ CONTROLS

PATIENT	*2k* HR URINE VOL. (ml.)	URINE FLOW RATE (ml/min/1.73®)	SERUM OSMOLALITY (mOsm./kg.)
Lu c^	950	1.3	308
C5	1250	1.71	298
C6	17^0	2.18	302
C7	1300	1.9	262
c8	720	1.31	2 *6k*
99	-	-	-
C10	700	1.08	260
C11	1200	2.06	-
C12	1050	1.86	-
C13	1250	1.53	288
C1**	1150	1.73	*27k*
C15	1020	1.65	279
C16	650	1.18	280
017	800	1.23	285
MEAN		1.59+ 0.3^	282+ 22

The difference between the means was statistically significant, t = 2.66, P=0.02> 0.01.

I Also presented in tables V and VI are the values for serum osmolality measured at the time of the *2k* hour urine collection. There was no significant difference between the sicklers (mean 290+ 23 mOsm/kg) and controls (mean 282+ 22 mOsm/kg) t = 0.31, P 0.7.

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• rBKATININE CLEARANCE»

(a) Table VII shows the values for serum creatinine, urine creatinine and the calculated creatinine clearance for S.C.A. patients.

TABLE VII

CREATININE CLEARANCE IN

PATIENTS WITH SICKLE CELL ANAEMIA.

N = 21 _

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I PATIENT	SERUM CREATININE (mg/dl)	URINE CREAT. (mg/dl)	CREATININE CLEARANCE. (Ml/min/l.73m^2)
S1	0.3	30	59
32	0.4	40	128
S3	o.4	40	75
S4	0.7	40	94
S5	. 0.45	40	155
S6	. 0.3	40	58
S7	0.4	40	76
s8	o.44	30	140
S9	0.7	58	129
810	0.59	43	136
S11	0.56	54	117
S12	0.44	38	101
813	0.25	32	158
S14	0.3	35	82
S15	0.3	24	54
S16	0.9	56	57
S17	0.59	59	175
818	0.42	60	136
S19	0.49	44	127
sao	0.32	44	131
821	0.45	37	69
	o.4£+ 0.16	42.3+ 10.3	107+ 37.5

Creatinine clearance among these patients ranged from 5^- to 175 ml/min/l.73m^2 S.A. with a mean of 107+ 37*5.

(b) Table VIII show® the corresponding figures for the controls. The range for creatimine clearance was 64 to 159 ml/min/l.73m^p with a mean of 132+ 35.

TABLE VIII

CREATININE CLEARANCE, I'H

CONTQRLS >

N = 13

(PATIENT	SERUM CREATININE (mg/dl)	URINE CREATININE (mg/d4)	CREATININE CLEARANCE. (ml/min/1.73m^2)
C4	0.3	35	138
S5	0.49	43	149
C6	0.93	27	64
C7	0.76	36	92
c8	0.37	26	90
C10	0.40	57	155
C11	0.50	30	123
C12	0.35	29	154
C13	0.54	56	159
C14	0.40	34	147
C15	0.62	47	123
C16	0.36	36	119
C17	0.61	49	98
MEAN	0.66+ 0.17	46.5+ 10.5	131.6+ 34.9

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COMMENTS:

(i) Statistical analysis showed no significant difference between the means for urine creatinine in the two groups, i • 1.007, P =0.3.

(ii) There was no statistically significant difference betwen the patients and controls in the levels of creatinine clearance (t • 2.01, P « 0.1>0.05).

(iii) There was no correlation between either creatinine clearance and serum creatinine (Coeff. of correlation « + 0.06) or creatinine clearance and urine creatinine levels (Coeff. of correlation = + 0.39)*

URINE CONCENTRATION

(a) * Table IX shows the concentration achieved by S.C.A, patients after a 12 hour period of fluid starvation. The mean urine concentration was 417 + 117 mOsm./kg.

(b) Also shown in table IX is the urine concentration achieved by the controls. The mean concentration was 622+ 117 mOsm./kg.

TABLE IX

URINE CONCENTRATION AFTER 12 HOUR FLUID RESTRICTION IN PATIENTS WITH SICKLE CELL ANAEMIA AND CONTROLS.

S.C.A. PATIENT	URINE CONCENTRATION (mOsmo/kg)	CONTROLS	URINE CONCENTRATION (m0sm$_o$/kg)
«1	320	C4	759
	453	C5	555
^{s}5	302	C6	453
Sk	266	C7	574
^{s}5	688	C8	675
^{s}6	54o	C10	560
^{s}7	526	C11	600
*8	424	C12	712
S_9	510	C13	651
S10	455	C14	812
S11	353	C15	593
S12	tySO	C16	646
S13	438	C17	508
S14	502		
S15	209		
S16	438		
$S1_7$	376		
S18			
SI9	367		
S20			
S21	305		
L ^ B A M	417 ± 117	MEAN	622 + 117

COMMENTS:

(i) Ihe difference between the means was statistically significant, t » 5.61, P= 0.001.

(ii) Patient S13 (S.0.2) developed recurence of pain and swelling of limbs at the end of the 12 hour dehydration period. He reported improvement 48 hours later after resumption of free oral fluid intake.

T A B L E X

COMPARISON OF RESULTS IN *THIS* STUDY WITH NORMAL REFERENCE VALUES FOR CHILDREN TWO YEARS TO PUBERTY

	PRESENT SUJDY S.C.A. PATIENTS	PRESENT STUDY CONTROLS	REFERENCE VALUES *
URINE VOLUME	275 - 1500 ml/day	650 - 1740 ml/day	500 - 1000 ml/day
SERUM CREATININE	0.3 - 0.7 mg/dl	0.3 - 0.9 mg/dl	0.3.- 0.7 mg/dl
URINE CREATININE	Mean 42mg/dl (l7mg/kg/day)	Mean 46mg/dl (20mg/kg/day)	8 - 2 2 nig/kg/day
CREATININE CLEARANCE	lo7± 37.5 ml/min/l.73m^2	131. 35 ml/min/1.73m^2	94 - 142 ml/min/1.73m^2
SERUM OSMOLALITY	260 - 310 mOsm./kg	260 - 308 mOsm./kg	298 - 308 mOsm./kg
URINE CONC. AFTERFLUID RESTRICTION	417 + 117 mOsm./kg	622 + 117 mOsm./kg	850 mOsm./kg

* Local laboratory values for normal children have generally not been worked out. Ihes«reference values are those from studies performed at the Department of Paediatrics and the Clinical Laboratories, University of Kentucky Medical Centre, Published in Nelson Textbook of Paediatrics, by Nelson, Vaughan, McKay and Bebrman (Eds) Eleventh Edition.
W.B.Saunders Co. Philadelphia, London, Toronto, 1979.

DISCUSSION AND REVIEW OF LITERATURE

This study attempted to demonstrate certain renal abnormalities associated with sickle cell anaemia using relatively simple and non-invasive techniques. What is currently known about those aspects which could not be investigated in this study is alluded to in this discussion and literature review.

URINE ANALYSIS.

Seven out of 21 patients with sickle cell anaemia in this study showed some abnormality of urine: three had slight protein; uria, two of whom also had macroscopic haematuria. The haematuria in these cases subsided spontaneously. Three other patients had pyuria, two of which were associated with significant bacteriuria.

Variable amounts of casts, red cells, white cells and traces of albuminuria have previously been noted in patients with sickle cell anaemia (10,14). These, however, cannot be regarded as specific for sickle cell anaemia. Haematuria which is frank, is significant and is probably the most conspicuous and most dramatic of the renal manifestations of sickle cell anaemia. It has been noted that the bleeding is generally painless, spontaneous and tends to be unilateral, occurring more frequently from the left kidney (15,16,17).

3he cause of haematuria is not yet completely elucidated. In patients who have had to undergo nephrectomy, histological examination has revealed a wide spectrum ranging from nothing specific through minor mucosal congestion to papillary necrosis (18). Akinkugbe (18) found that some cases of haematuria due to papillary necrosis could be diagnosed radiologically. Hie features which he felt were characteristic were "ring" changes in the renal papillae and cavities in the papillae or pyramids. Ihese findings have been corroborated by others (19).

The original association between papillary necrosis and diabetes suggested a relationship between the former and sepsis. Crone, Jefferson, Pillegi and Lowry (16) reported 8 cases of sickle cell trait haematuria, 3 of which were associated with proven urinary tract infection, and in one of whom bleeding ceased after infection was eradicated. In the two patients in this study who had haematuria, there was no clinical or laboratory evidence of infection.

Perillie and %>stein (20) found increased degrees of sickling in patients with sickle cell trait and anaemia in the presence of a hypertonic medium. They postulated therefore, that the hypertonicity at the tips of the renal papillae led to increased sickling and stasis resulting in ischaemic necrosis of the papillae.

It has been stressed that haematuria occurred more commonly in the sickle cell trait than in sickle cell anaemia, with rates for the homozygous state reportedly varying from *1%* to 10% in different series.Others (21) feel that this apparently higher incidence in the trait is probably unreal, considering that sickle cell trait occurs about 40 times more frequently than sickle cell anaemia.

Konotey-Ahulu (22) working in Ghana for more than a decade in an area with a trait population of more than 120,000 reported no cases of renal infarctive haematuria in trait patients. Although Kenyatta National Hospital is not situated in the heart of our sickle cell population, there is nevertheless a sizeable population of sickle cell carriersin Nairobi as evidenced by the number of sicklers attending the haematology clinic (300-500) per year) Here also there have been no cases of haematuria attributable to sickle cell disease (23). It seems possible that some other factors may be responsible for this apparent variation in the incidence of sickle cell haematuria. An interesting recent finding is of sickle cell haematuria in patients who also had haematological features consistent with von Villebrand's disease. None of those patients had bleeding from any other site and they all improved on therapy with normal plasma (24).

Spontaneous recovery from sickle cell haematuria is a characteristic finding. However it has been found necessary in some cases to perform nephrectomy for persistent or recurrent haematuria (l8,25). Recently Pawaroo and Douglas (26) reported successful, use of conservative surgery with partial renal resection after I.V.P. and nephroscopy, in the management of sickle cell haematuria. That is an important development since total nephrectomy on one side does not preclude recurrence of haematuria from the remaining kidney at a later date.

Two (9%) of the sicklers in this study had significant bacteriuria. The small sample in this study makes it hazardous to make generalizations. However in a study performed in the same hospital by Shah (27) in 1976 he found an overall prevalence rate of urinary tract infection in children aged 1 week to 6 years of 3.596. ^{x}n those with malnutrition the rate was 12%.

High Incidence of pyelonephritis in association with sickle cell anaemia and trait has been reported in various studies (10,28,29*30). The pathophysiological basis for the increased susceptibility to pyelonephritis in SCD is probably the same as for the known proneness to infection by Streptococcus pneumoniae (31,32) and Haemophilus influenzae (33) organisms These patients have been found to be deficient in the opsonic adherence that enhances phagocytosis of pneumococci (3A)^due to a defect in the alternate pathway of complement activation T35).

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A L B U M I N U R I A

None of the patients in the present study demonstrated proteinuria consistent with the nephrotic syndrome. In the absence of histological and immunological examination, further comment on the significance of the slight proteinuria, macroscopic haematuria and urinary casts seen in these patients is not possible.

A few cases of typical nephrotic syndrome in association with SCD have been reported by Sweeney, Dobbins and Etteldorf (8) and by Behrman and TUblin (36). Ihey were characterised by normal serum cholesterol levels and variable glomerular destruction on histology. The patients in the former series responded to corticosteroids while those in the latter did not.

Electron microscopic studies in ordinary sicklers without renal disease (37) and in those with the nephrotic syndrome (38) have failed to show a direct relationship between SCD and the nephrotic syndrome observed in some patients. Such relationship still remains possibly coincidental.

URINE OUTPUT

The data in tables IV and V show that patients with sickle cell anaemia generally had lower urine outptilt and urine flow rate than the controls.

Since these patients were on a free fluid intake regime it can be construed that the patients either had a small Huid input or were just more dehydrated than the controls.

Serum osmolality measurements done at the same time showed a tendency for the sicklers to have a higher value than the controls. These findings suggest that dehydration was probably a factor in the production of diminished urine flow among the sicklers.

These results concur with those of Addae (39) who compared urine flow rates in sicklers in crisis with those of non-crisis sicklers and with normal controls (ages 15-27 years). H_e found that the mean flow rate in non-crisis sicklers was about twice that in controls or sicklers in crisis. He also found a tendency for plasma osmolality to be higher in sickle cell crisis than in the non-crisis state.

In a study by Hatch and Diggs (40) it was shown that a remarkable weight lossoccurred in sicklers prior to the onset of crisis. They also found that not only did patients in sickle cell steady state produce above normal amounts of urine, but half of the patients produced urine volumes that were greater than their average daily fluid intakes. Such patients were obviously in danger of getting severely dehydrated in case of significant fluid restriction.

It is likely that reduced fluid intake and resultant dehydration leading to sluggish blood flow and haemoconcentration predispose the patients to increased sickling and may precipitate crises.

A common prescription for sicklers admitted to our hospital in crisis advises "plenty of oral fluids[11]. This leaves the amount and frequency of fluid administration at the discretion of the nurse or the patient. It is unfair on the patient who may be too sick or anorexic to take the initiative to drink lots of fluid. A more accurate clinical assessment of dehydration and a deliberate decision on fluid requirement seems mandatory in these cases.

CREATININE CLEARANCE

In the present study all the patients were sicklers in crisis. Although the GFR in sicklers and controls showed no statistically significant difference there was a tendency towards lower GFR in the sicklers.

A feature that has been consistently demonstrated in various studies is a markedly elevated glomerular filtration rate in non-crisis sickle cell patients (11,14). Ihe GFR ha been found to be raised upto 71%above normal control levels.

Addae (39) found a markedly reduced GFR in crisis patients compared to non-crisis sicklers and normal controls. H_e suggested that dehydration in sickle cell crisis led to a reduced fluid volume reaching the distal nephron. This in turn led to a reduced GFR and reduced urine output.

Studies in adult sicklers (41) have shown that the high GFR seen in young sicklers reaches a peak and then tends to drop after the age of 20 years. However in some cases high GFR has persisted in patients over the age of 40 years (21). Histological examination in sicklers with high GFR has shown that there is vascular engorgement with sickled erythrocytes and marked dilatation of vascular loops at the glomerular hilus (42). Ihese changes are considered responsible for the increased renal blood flow and GFR in young patients. With advancing age progressive glomerular hyalinization occurs and leads to the reduced renal blood flow and GFR seen in adult sicklers.

URINARY CONCENTRATION

Following a 12 hour period of fluid restriction patients with sickle cell anaemia in this study achieved a mean urine concentration of 417 + 117 mOsm./kg. compared to the control mean of 622 +. 117. mOsm./kg. The difference between the means was statistically significant at P = 0.001.

The impared concentrating ability shown in the sicklers agrees with results from other studies (12,43,44,45). However in all these other studies antiduiresis was induced with vasopressin. and the urine concentration among controls was higher than obtained in this study.

Attemps have heen made to explain the basic defect in the sickle cell kidney responsible for the impaired concentration of urine, Keitel, Thomson and Itano (45) considered that anaemia and haemoglobinaemia could be responsible, but the finding that similar impairment of concentration occurred in individuals with sickle cell trait in the absence of anaemia or haemolysis, made this proposition untenable. Those workers (45) had demonstrated that the concentrating defect in sicklers was improved by multiple transfusions which reduced the amount of circulating haemoglobin $• They also noted that the severity of the defect and its reversibility was altered with age; the defect was more serious in older patients and transfusions had a less significant effect in such patients. They proposed that the concentrating defect might be due to subclinical intravascular sickling in the kidney or to functional impairment of the concentrating mechanism by haemoglobin S in the tubular cells.

Perillie and Epstein (46) studied the effects of a hypertonic medium upon erythrocytes from patients with sickle cell anaemia, those o with the trait and from individuals with normal haemoglobin. Ihey observed intantaneous sickling in all cases of sicklers, half of the traits and none of the controls. The^ study also showed increased viscosity of the blood under those circumstances, but only in sicklers. Biey concluded that the hypertonicity that is present in the renal medulla and papillae led to sickling of red cells and increased blood viscosity. These in turn led to reduced blood flow in the medulla, reduced oxygen availability and reduced sodium reabsorption into the interstitiilm. A hypotonic interstitium would make it difficult to concentrate urine.

Angiographic studies (42) have demonstrated some associated structural defects. The vasa rec^a in sickle cell anaemia kidneys have been shown to be markedly reduced in numbers, misshapen, dilated and some obliterated. Ihe vascular architecture in the cortical regions of the kidneys remained relatively normal. Ihe resulting functional defect has been aptly compared to the beaver kidney which has no equivalent of the human renal medullary function and is unable to concentrate urine above 500 mOsm/kg. This profound structural abnormality can explain the increasing severity and the reduced reversibility that occurs with increasing age of patients.

CONCLUSION

1. Many of the features of renal disease in children with sickle cell anaemia are occult and can only be demonstrated by laboratory tests in asymptomatic patients. Simple urine analysis and culture demonstrated a higher incidence of abnormality in sicklers than in controls. Mild degrees of haematuria not requiring active treatment were noted.

2. Proteinuria consistent with the nephrotic syndrome was riot found.

3. Patients admitted to hospital in sickle cell crisis were shown to be significantly dehydrated as shown by a marked reduction in urine flow rate and urine volumes.

4. Patients with sickle cell anaemia in crisis were shown to have a lower glomerular filtration rate than controls. This is in contradistinction to findings in other studies which showed markedly elevated GFR in non-crisis sicklers.

5. It has been demonstrated that sicklers have a marked impairment in their ability to concentrate urine.

RECOMMENDATIONS

1. In the management of sicklers in crisis, the state of fluid balance is of cardinal importance and should be given due consideration as it may significantly influence the severity and duration of illness.

2. A prospective, large sample study to determine the incidence and prevalence of pyelonephritis among children with sickle cell anaemia may provide useful information on the relationship between the morbidity in SCD and such infection.

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