Serum and Urinary Creatinine in Children with Severe Protein Malnutrition

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IN Central America[1] as in Jamaica[2] and Africa,[3] children suffering from the severe protein deficiency of kwashiorkor have been found to have a very low urinary output of creatinine. Standard et al.[2] found that during recovery urinary creatinine increases proportionally to the increase in muscle mass. However, about half of their patients and most of ours showed an abrupt transient rise in creatinine excretion during the first few days of treatment, followed by a variable drop, a phenomenon which seemed more marked in children with edema. This suggests that urinary excretion of creatinine in the acute phase of kwashiorkor may be temporarily reduced by factors other than decreased muscle mass. In this case urinary excretion of creatinine could not properly be used to estimate relative muscle mass of children with severe protein malnutrition. If children with kwashiorkor can be shown to have a reduced renal capacity to eliminate endogenous creatinine, this would explain the marked transient rise frequently observed when treatment is initiated. The present study measures the urinary excretion of creatinine and the serum creatinine concentration of children during the acute phase of kwashiorkor and at intervals during recovery. Creatinine clearances were also calculated and compared with data obtained from clinically healthy adequately nourished children.

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MATERIAL

Children with Kwashiorkor

Nine children hospitalized with kwashiorkor were studied. Their initial age, total serum proteins, body surface and twenty-four-hour urine volume are included in Table I. All had severe hypoproteinemia and edema, although in one child (PC-95) the edema was mild. Severe oliguria was present in one child (PC-100), and to a lesser degree in two others (PC-102 and PC-103). With adequate protein therapy all showed satisfactory initial recovery, during the period of observation. The initial decrease in body surface seen in all but one case (PC-67), was due to the disappearance of edema. In the five children in whom the observation period was prolonged beyond the initial few days, the characteristic return of the total serum proteins to normal levels occurred.

Well Nourished Control Children

Seventeen children were selected from a private school. They belonged to the upper socioeconomic group of Guatemala City, and according to physical measurements and clinical examination were well developed and in good health. Their age, total serum proteins, body surface and three-hour urine volumes are included in Table II.

METHODS

The children with kwashiorkor were placed in a bed specially adapted for complete urine collection, while the control children voided

TABLE I
Urine and Serum Creatinine Changes in Children Recovering from Kwashiorkor

Subject	Age	Days from Admission	Body Surface (M.²)	Serum Protein (gm./100 ml.)	Hematocrit (%)	Urine Volume (ml./24 hr.)	Creatinine		
							Urine (mg./24 hr.)	Serum (mg./100 ml.)	Clearance (ml./min./M²)
PC-82	1 yr. 3 mo.	0	0.44	3.92	27	424	54	0.68	13
		7	0.40	5.09	28	618	80	0.54	26
PC-66	1 yr. 6 mo.	0	0.41	3.64	31	683	49	0.76	11
		12	0.40	4.68	31	536	66	0.49	24
PC-67	1 yr. 6 mo.	0	0.37	4.69	27	555	51	0.44	23
		8	0.37	4.75	31	694	69	0.38	29
PC-98	2 yr.	0	0.45	3.29	29	301	68	0.79	13
		8	0.41	4.42	26	101	78	0.72	18
		35	0.43	7.02	..	590	120	0.55	35
		105	0.48	6.65	..	336	118	0.46	38
PC-103	2 yr. 8 mo.	0	0.45	3.96	35	112	64	0.75	13
		5	0.44	4.00	31	123	86	0.54	25
		21	0.44	6.90	..	703	56	0.56	16
		63	0.51	7.33	..	918	148	0.57	35
PC-95	2 yr. 9 mo.	0	0.47	3.57	30	182	66	0.88	11
		12	0.44	4.77	24	863	89	0.47	30
		35	0.47	5.81	..	344	84	0.47	33
		180	0.56	7.40	..	700	181	0.49	35
PC-100	3 yr. 10 mo.	0	0.51	2.83	37	36	45	0.91	7
		6	0.48	3.70	30	44	67	0.31	31
PC-102	4 yr. 8 mo.	0	0.63	3.13	34	76	144	1.07	15
		13	0.59	5.45	34	850	195	0.72	32
		30	0.64	6.41	..	367	246	0.52	51
PC-101	5 yr.	0	0.57	3.05	36	405	111	0.80	17
		20	0.54	4.40	37	625	125	0.65	25
		45	0.57	6.33	..	845	154	0.57	33
		90	0.63	6.28	..	586	158	0.48	36

voluntarily. The urine was preserved with toluene and stored at minus 20°c. until analyzed. Blood was obtained by pricking the fingertip or by venipuncture sometime during the urine collection period, the serum separated and kept at minus 20°c. Creatinine was determined by the method of Clark and Thompson[4] in both the urine samples and in tungstic acid filtrates of the serums. Total serum proteins were determined by the density gradient method of Lowry and Hunter.[5] Body surface area was calculated from height and weight data employing the equation of Boyd and Scammon.[6] Clearances were calculated by the equation $U \times V/S$ in which U and S are the concentrations of creatinine in urine and serum per 100 ml., respectively, and V is the volume of urine per minute. The collection periods were as close as possible to three hours for the control children and twenty-four hours for the patients with kwashiorkor.

RESULTS

The data in Table I indicate a rapid rise in the twenty-four-hour urinary excretion of creatinine and a simultaneous fall in serum creatinine concentration during initial recovery from kwashiorkor. With the exception of one child (PC-98), the fall cannot be accounted for by hemodilution as estimated from changes in hematocrit. Also shown in Table I are the renal clearances expressed per square meter of body surface, which were markedly reduced on admission to the hospital and which increased rapidly during the first few days of therapy.

Renal clearance values obtained in five of the patients with kwashiorkor after at least

TABLE II
Urine and Serum Creatinine in Healthy Children

Child	Age	Total Serum Protein (gm./100 ml.)	Body Surface (M^2)	Urine Volume (ml./3 hr.)	Creatinine		
					Urine (mg./3 hr.)	Serum (mg./100 ml.)	Clearance (ml./min./M^2)
R. R.	6 yr. 5 mo.	6.65	0.77	105	45	0.83	42
J. H.	6 yr. 7 mo.	6.40	0.88	115	51	0.62	56
J. W.	6 yr. 9 mo.	6.51	0.83	90	49	0.83	43
A. S.	7 yr. 1 mo.	6.40	1.07	57	66	0.88	37
B. E.	7 yr. 3 mo.	7.25	0.87	135	59	0.73	50
F. N.	7 yr. 3 mo.	6.75	1.17	218	71	0.76	44
H. A.	7 yr. 4 mo.	6.50	0.84	69	60	0.81	50
G. A.	7 yr. 5 mo.	6.65	0.94	30	41	0.69	33
A. L.	7 yr. 5 mo.	7.10	0.83	91	54	0.81	47
L. M.	7 yr. 8 mo.	6.65	0.95	143	66	0.74	51
A. F.	7 yr. 11 mo.	6.50	0.83	47	43	0.86	35
J. C.	8 yr. 2 mo.	6.75	1.03	101	73	0.91	44
L. Mo.	8 yr. 3 mo.	6.70	0.90	79	66	0.79	51
F. P.	8 yr. 4 mo.	6.52	1.03	48	77	0.88	43
Jo. W.	8 yr. 7 mo.	6.52	0.94	125	67	0.84	47
S. O.	8 yr. 7 mo.	7.25	0.88	34	55	0.79	45

thirty days of therapy are given in Table I and those for clinically healthy, well nourished children are shown in Table II. These data indicate that as early as one month after initiation of treatment, the children recovering from kwashiorkor reach clearance values similar to those of the control children. The serum creatinine concentration of the children with kwashiorkor, not only decreased during the first few days of therapy, but also remained markedly lower than the serum creatinine levels found in the control children.

COMMENTS

It is not conceivable that the lean body mass could increase so markedly in so short a time as to explain the rapid rise in the urinary excretion of creatinine. Furthermore, the parallel decrease in the serum creatinine levels, indicates a relative initial retention of creatinine. It is striking that the impairment in creatinine excretion in the patients studied was so readily reversed during initial recovery.

The fact that in adults, the endogenous creatinine clearances and inulin clearances are equivalent,[7] is evidence that creatinine is excreted by glomerular filtration and that tubular reabsorption does not occur. In the present study, creatinine clearance values obtained by us in normal children averaged 44 ml. per minute/M^2. This is 64 per cent of the clearance reported by Sirota et al.[8] of 69 ml. per minute/M^2 for the adult subject, and 68 per cent of the average values found by us for eighteen clinically healthy male adults twenty to thirty-five years of age (65 ml./minute/M^2).[9] Broad and Sirota[7] studied four infants, two months to twenty-five months of age, and found (in agreement with our results) that their endogenous creatinine clearance was only about 60 per cent of the inulin clearance. These authors speculated that in infants the "picric acid-chromogenic material" measured by the method employed, is excreted by the kidney in a different manner than in adults, an explanation which could well apply to our findings for normal children. Nevertheless, the extremely low clearances found in children with acute kwashiorkor indicate an even more reduced renal excretion of creatinine which could be due to either tubular reabsorption, decreased glomerular filtration rate or reduced renal plasma flow. Although the normal tubules do not reabsorb endogenous creatinine, such a mechanism might come into play in the protein-depleted child. On the other hand, functional impairment of the glomeruli and reduction in renal plasma flow

are suggested by the findings of Gordillo et al.[10] that the clearance of inulin as well as that of para-amino hippuric acid are decreased in severe chronic infantile malnutrition.

Standard et al.[2] have pointed out the association between the transient initial changes in creatinine excretion in children with kwashiorkor and the loss of edema. In the present investigation all the children studied had edema on admission to the hospital, and loss of edema invariably accompanied the changes in serum and urinary creatinine. It is possible that the renal impairment which is causing the retention of creatinine is also contributing to the formation of edema. Parallel studies of severely malnourished children without edema, i.e., marasmus, might be helpful in evaluating this possibility.

No explanation has been found for the observed persistence of very low serum creatinine concentrations in children after recovery; the duration of this effect and the severity of protein malnutrition necessary to produce it are under investigation in our laboratory. The immediate practical implication of the results described is that the values for creatinine excretion obtained in children with acute kwashiorkor are not valid for comparative estimations of the increase in muscle mass during early recovery.

SUMMARY

Nine children hospitalized with kwashiorkor had very low initial urinary excretions of creatinine which increased sharply during the first week of treatment. The magnitude and rates of these increases were too great to be accounted for by a change in muscle mass. The initial serum creatinine concentrations, although not initially elevated, decreased markedly parallel to the increase in urinary excretion. Endogenous creatinine clearances per square meter of body surface were consequently very reduced on admission and increased rapidly during the first week of treatment.

In patients followed up for periods varying from two to six months after initiation of treatment and who were clinically recovered, serum creatinine levels remained much lower (0.46 to 0.57 mg. per 100 ml.) than the average for a group of sixteen well nourished control subjects (0.78 mg. per 100 ml.). The average clearance for the latter children was only 68 per cent of the value found for healthy adults; it appears therefore, that creatinine clearance in children does not represent true glomerular filtration.

A practical conclusion from the results is that the figure for twenty-four-hour urinary excretion of creatinine during or soon after the acute phase of kwashiorkor, is not reliable for the estimation of muscle mass.

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