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TRANSIENT AMINO-ACIDURIA IN SEVERE POTASSIUM DEPLETION

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Severe potassium depletion can produce gross clinical disturbance with weakness, paralysis, and mental confusion. The condition can arise in primary renal disease (Schwartz, 1955) and also from extrarenal causes (Black, 1957). Confusion arises because potassium loss from extrarenal causes can result in renal dysfunction with albuminuria and impaired ability to concentrate or excrete an alkaline urine (Relman and Schwartz, 1956).

Urinary amino-acid loss has been described in the nephrotic syndrome (Blainey, 1954; Tegelaers and Tiddens, 1955; Stanbury and Macaulay, 1957), and in the tubular nephropathies (Milne, Stanbury, and Thomson, 1952; Bickel, Smallwood, Smellie, and Hickmans, 1953).

The case reported here showed, in association with potassium depletion, gross amino-aciduria which disappeared on correction of the potassium deficit.

Case Report

A 72-year-old woman was admitted to hospital as an emergency with the sudden onset of confusion and weakness

12 hours previously. A history was obtained from her relatives of cough, sputum, and breathlessness for 12 years, with intermittent ankle oedema for four weeks. Albuminuria had been noted in hospital seven years previously (acute bronchitis), but not one year previously (pneumonia). The patient had been taking digitalis since 1951 and had had 5 g. of chlorothiazide over the five days prior to admission. Diet was adequate and included two cooked meals with first-class protein and green vegetables daily. She had had no diarrhoea nor did she use purgatives.

On examination she was confused and drowsy. The mouth temperature was normal, the respiratory rate was 18 a minute, and she had a regular pulse rate of 66 a minute, with occasional extrasystoles. The arterial blood-pressure was 170/90 mm. Hg, and her heart was slightly enlarged, with, on auscultation, an apical grade II systolic murmur which had been noted in 1951. A few scattered rales were heard at the lung bases and there was slight pitting oedema of the ankles. Apart from her abnormal mental state, clinical examination of the central nervous system showed nothing abnormal, and no abnormality was found in any other system.

Extensive routine haematological and biochemical investigation showed no abnormalities except in the levels of serum electrolytes, which were Na, 105 mEq/l.; K, 3.8 mEq/l.; and Cl, 73 mEq/l. There was no respiratory acidosis present as judged by arterial CO₂ content and pH, and liver-function tests and oral glucose tolerance were normal.

Chest radiography suggested that the lungs were emphysematous and that the left ventricle was enlarged. The first electrocardiogram showed prolongation of the Q-T interval and prominent U waves. The urine showed no albumin or sugar and no formed elements at any time, but the specific gravity was fixed between 1009 and 1011 for at least the first 17 days after admission. The main abnormalities are recorded in Table I.

TABLE I.—Findings During Potassium Depletion and After its Repletion

Features	During Potassium Depletion	After Treatment ¹	Comments
Serum Na (mEq/l.) ..	105	130	
" K " ..	3.8	4.2	
" Cl " ..	73	100	
E.C.G.: Q-T c.sec. ..	0.47	0.41	Progressive shortening of Q-T c. and disappearance of U waves. Lead V ³ used throughout
U waves ..	Prominent	Absent	R.B.C. chloride and sodium both fell with treatment
R.B.C. potassium mEq/l. R.B.C. ²	78 (Day 1)	99 (Day 35)	
Muscle intracellular potassium ³ mEq/l. intracellular water	155.6 (Day 1)	175.8 (Day 37)	
Muscle intracellular potassium ⁴ mEq/kg. dry weight	324.0 (Day 1)	433.0 (Day 37)	
Muscle intracellular acidosis	Present	Absent	High intracellular chloride taken to indicate acidosis ⁴
Urinary excretion of potassium	<Intake	≈ Intake (Day 35)	
Amino-aciduria ..	Significant (Day 11)	Normal (Days 32, 33, and 85)	See Table II
Maximum specific gravity of urine	1.010	1.016	
Albuminuria ..	Nil	Nil	
Creatinine clearance, ml./min.	75 (Day 10)	53	Over a four-hour period
Clinical condition ..	Confused, weak, paranoid	Mentally clear and co-operative; no weakness	

¹ Day 43 unless otherwise stated.

² Mean normal value = 98.2 mEq/l. R.B.C. (Flear, Hughes, and Quinton, 1958).

³ Mean normal value for intracellular potassium = 154.4 mEq/l. intracellular water (Crampton, Flear, and Matthews, 1960).

⁴ Mean normal value = 329.7 mEq/kg. dry weight (Crampton *et al.*, 1960).

⁵ Inulin space taken as measure of extracellular space (Crampton and Flear, 1958).

Diagnosis, Treatment, and Course

Definite diagnosis of potassium depletion is difficult, and in practice a provisional diagnosis is usually made from the simultaneous occurrence of a number of non-specific findings (Flear, 1958), or from a history suggesting potassium loss or deficient intake.

Though a careful appraisal of the clinical history and past treatment in this case failed to suggest any obvious reasons for potassium depletion,* the electrocardiographic pattern was suggestive of potassium deficiency and the serum electrolyte pattern was compatible with this diagnosis. The mental state also pointed to some severe metabolic disturbance, and a diuretic known to cause potassium loss had been given.

The serum potassium level was within normal limits, but serum potassium levels are unreliable in the detection of cellular potassium depletion (Moore, Edelman, Olney, James, Brooks, and Wilson, 1954; Burrows and Ross, 1956; Flear *et al.*, 1957).

Confirmatory evidence was sought by muscle biopsy, and though this did not show a lowering of intracellular potassium content or concentration (see Table I), it also does not exclude potassium deficiency (Flear, 1958). The muscle biopsy suggested the presence of intracellular acidosis, another finding compatible with potassium depletion. The R.B.C. potassium at 78 mEq/l./cells was definitely low, a finding we have not observed except in potassium depletion.

On the basis of these abnormalities a therapeutic trial of potassium therapy was decided upon and treatment with potassium supplements was followed within four days by rapid clinical improvement with disappearance of mental confusion, increase in strength and well-being, loss of oedema, and the development of a voracious appetite. These changes were accompanied by

Changes in serum sodium and red-cell potassium while receiving added potassium. The patient was grossly confused and psychotic when treatment was begun and for several days thereafter. Serum potassium levels were within the normal range except for a rise to 6.7 mEq/l. during the five days of very heavy potassium supplements.

progressive return of the E.C.G. and serum biochemistry towards normal (see Fig.). Serum potassium levels showed a significant upward trend from 3.8 mEq/l. (day 1) to 5.7 mEq/l. on the 27th day of treatment.

One of us (K. W. D.) had suggested a renal tubular defect as the cause of the potassium loss and that amino-aciduria should be looked for. Dr. J. D. Blainey kindly carried out this investigation, and gross amino-aciduria was found (Table II).

A strong point against the diagnosis of a primary renal tubular dystrophy as the cause of the potassium loss was the continuous retention of potassium as shown by daily fluid and electrolyte balance charts.† In addition there were no associated abnormalities such as glycosuria, proteinuria,

*The amount of chlorothiazide (5 g.) which had been given was thought to be far too small for the diuretic to be entirely responsible for the potassium depletion.

†Full details of the 24-hour urinary output of electrolytes and fluid balance can be supplied to any interested reader.

TABLE II.—Pattern of Amino-aciduria Found on Paper Chromatography

Amino-acids	Day 11	Days 32 and 33	Day 85
Cysteic acid	Trace	Trace	Trace
Glycine	++	+	..
Serine	++	—	..
Taurine	+	+	—
Glutamic acid	++	—	—
Proline	++	—	Trace
Histidine	Trace	—	..
Valine	..	—	..
Lysine	++	—	—
Arginine	++	—	—
Glutamine	+++	—	—
Threonine	++	—	—
Alanine	++	Trace	Trace
Tyrosine	..	—	—
Leucine	Trace	—	—
β -Hydroxy-n-butyric	+-	—	—

Total 24-hour urinary output. By comparison with taurine standards: Trace = 5 μ g.; + = 5 μ g.; ++ = 10 μ g.; +++ = 20 μ g.

cystinuria, or corneal cysteine deposits, one or more of which usually accompany primary tubular defects.

By the 27th day of treatment, during which time 4,300 mEq of potassium had been given as supplements to a normal ward diet, the serum sodium had stabilized around 125 mEq/l. (see Fig.). The urinary findings suggested that potassium supplements were still being retained while sodium intake and excretion approximately balanced. To establish whether this low serum sodium level was the normal for this patient, and further to decide whether potassium deficiency was still present, potassium supplements were increased to 360 mEq/day for five days (days 30–35) then sodium supplements of 299 mEq/day were substituted for the potassium for four days while fluid intake was kept constant; finally all supplements were stopped.

On added potassium the urinary potassium remained considerably lower than intake until the fifth day. During sodium supplements on a fixed fluid intake, marked thirst was experienced and the serum sodium level rose to 130 mEq/l., while most of the added sodium was excreted in the urine. Without supplements the serum sodium level and urinary sodium excretion reverted to pre-trial levels while loss of potassium in urine fell to low levels.

Further urinary chromatograms at this stage showed that the abnormal amino-aciduria had disappeared.

These findings suggested: (1) the persistence of some potassium depletion, at least until the fifth day of the large potassium supplements (day 35); (2) the absence of significant sodium depletion; (3) that the patient's normal serum sodium level was low (see Fig.) (and compare the values at out-patient follow-up on day 85; Na = 127 mEq/l., and one year later Na = 130 mEq/l.); and (4) that the potassium loss was not due to primary renal disease.

A second muscle biopsy and further studies on whole blood and red cells (Table I) confirmed the retention of potassium which had taken place.

Discussion

The total amount of potassium given as supplements over 35 days was 6,640 mEq. This was in addition to the intake of potassium in a normal ward diet. Faeces were not analysed for potassium, but the patient had no diarrhoea, and it is unlikely that significant amounts of potassium were lost by this route. Daily faecal loss measured for 83 days in four patients on high potassium intake and without diarrhoea has ranged from 3.25 mEq/day (mean 9.4 mEq).

The lowering of total red-cell and muscle potassium had been of the order of 25%, as shown by the amount of potassium retained.

The outstanding interest in this case was the occurrence of gross amino-aciduria, without glycosuria, during the period of potassium depletion (Tables I and

II). At this time also the early morning urine was of low and fixed specific gravity. After potassium repletion both these findings disappeared.

Denton, Wynn, McDonald, and Simon (1951) have reported two cases in which a similar amino-aciduria occurred during potassium depletion. Neither had glycosuria. In one of their two patients' treatment with potassium abolished the amino-aciduria; the other patient died while still depleted of potassium.

In his recent review Stanbury (1958) draws attention to the fact that amino-aciduria has resulted from severe and acquired renal tubular disturbances and that it has on occasion been reversible. We feel that the amino-aciduria in our patient was caused by a renal tubular disturbance for which the potassium deficiency was responsible. This interpretation is supported by the normal liver-function tests, by the low and fixed specific gravity of the urine at the time of amino-aciduria, and by the disappearance of the urinary abnormalities on correction of the potassium depletion. In the patient with nephrotic syndrome and both amino-aciduria and potassium depletion, reported by Stanbury and Macaulay (1957), treatment with potassium had no effect on the amino-aciduria. In their patient potassium depletion had been present for much longer than in our patient or those reported by Denton *et al.* (1951).

It is submitted that the possibility of potassium depletion and/or intracellular acidosis should be considered in every case of amino-aciduria and also that amino-aciduria should be looked for when potassium depletion is suspected.

Summary

A case is presented in which potassium depletion was accompanied by significant amino-aciduria, which disappeared with potassium therapy.

Attention is also drawn to the difficulties attendant upon a definitive diagnosis of potassium depletion, and it is again emphasized that normal serum potassium levels can be misleading.

Possible implications of the findings are discussed.

Thanks are due to Dr. J. D. Blainey (department of experimental pathology) for assessment of amino-aciduria, and to Drs. R. F. Crampton and D. Matthews (department of physiology) for help with the muscle biopsies. Other investigations were carried out by the department of biochemistry at the Queen Elizabeth Hospital.

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PROPHYLACTIC USE OF ORAL PENICILLIN IN RHEUMATIC FEVER, CHOREA, AND CARDITIS

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We have attempted to show the actual occurrence of rheumatic manifestations, intercurrent respiratory infections, and laboratory evidence of streptococcal infection in children suffering from heart disease and given penicillin prophylactically. At the St. Joseph's Children's Heart Hospital, Rainhill, under the devoted care of nursing and teaching sisters, their treatment and progress have careful and close surveillance. Three physicians regularly attend the hospital, so that each child is usually seen once in the course of each week and more often when necessary. The 40 beds are occupied mainly by children suffering from rheumatic heart disease, but there are also a few children who have congenital heart lesions. No attempt at a statistical study or a comparison of the effects of penicillin V with penicillin G has been made because the series is too small.

For the first year of the trial prophylaxis had not been given and the results are analysed under the heading of "control period." In the second year penicillin V tablets, 60 mg. b.d., were used; these tablets were taken on an empty stomach with the sister present at the bedside. A similar procedure was followed throughout the third year, penicillin G tablets, 200,000 units b.d., replacing the penicillin V.

The clinical progress of each child was commented on independently by each physician. Throat swabs were taken from every child at fortnightly intervals, and these were cultured, typed, and grouped at the Royal Southern Hospital. The delay between taking the swab and culturing it was between one and a half and two hours, but we first proved to our own satisfaction that under the particular circumstances the streptococcus group A will survive for much longer periods than this.

Blood was also taken from every child at fortnightly intervals and estimations were made of the erythrocyte sedimentation rate and the anti-streptolysin O (A.S.O.) content. With the kind co-operation of Distillers Company Ltd., the majority of specimens of blood were also forwarded to their laboratories, where the penicillin content was estimated.

Clinical Findings

TABLE I.—Manifestations of Acute Rheumatism

	No. of Cases	Rheumatic Fever	Chorea	Carditis	Total
Control period	38	5	3	0	8
Penicillin V ..	40	4	2	1	7
„ G ..	39	1	1	1	3