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A Case of Hb S/A-α-thalassemia Exhibiting Quadriplegia Due to Distal Renal Tubular Acidosis

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ABSTRACT. A 46-year-old negro seaman who called at Port Mizushima, Kurashiki City, from West Africa on May 21, 1981 developed quadriplegia shortly after having taken a tablet of an antipyretic agent on the ship. At the Port Clinic in Mizushima, hypopotassemia was detected and Guillain Barré syndrome was suspected. Adrenocorticosteroids therapy was started, but he became dyspneic because of the progression of the paralysis up to the level of respiratory muscle. He was, therefore, transferred to our emergency center and hospitalized. On the sixth hospital day (May 27), clinical manifestations improved by intravenous administration of potassium.

Diagnosis of distal renal tubular acidosis was entertained on the basis of the presence of metabolic acidosis, hypopotassemia and the absence of acidification of urine by short duration NH_4Cl acid-loading test. The hematological studies revealed a combination of sickle cell trait (Hb S/A) with α-thalassemia trait.

It is well known that sickle cell anemia (Hb S/S) occasionally causes secondary distal renal tubular acidosis. However, the occurrence of renal tubular acidosis in sickle cell trait (Hb S/A) and in α-thalassemia trait (αTh/A) has not yet been reported in the literature. It is therefore thought that our observation on this case will deserve special description as one of the possible clinical signs of sickle cell trait.

Key words : distal renal tubular acidosis — quadriplegia — hypopotassemia — α-thalassemia trait — sickle cell trait

Renal tubular acidosis (RTA) is a syndrome characterized by functional defect of acid secretion through the renal tubules, chronic hyperchloremic acidosis and hypopotassemia leading to quadriplegia.[1,2)]

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A negro male patient of RTA exhibiting quadriplegia and dyspnea due to severe hypopotassemia was recently encountered in our clinic. Routine hematological-chemical examinations and hemoglobin studies disclosed that he had sickle cell trait (Hb S/A) in combination with α-thalassemia trait (αTh/A) as pathological basis of his illness.

The purpose of this paper is to describe the clinical symptoms and signs of this interesting patient and to review the literature on RTA in sickle cell diseases.

CASE REPORT

A 46-year-old negro seaman from West Africa was admitted to the Port Clinic in Mizushima on May 21, 1981, because of motor weakness. He had a history of mild weakness in his extremities after he was operated on for left renal calculi when he was 15 years old. On May 19, 1981, he had high fever at sea, a ship's doctor gave him one tablet of an antipyretic agent. Motor paralysis began to appear in his legs and extended upwards in a short time after his temperature fell down. On May 21, 1981, at the Port Clinic he was found out to be hypopotassemic and he was suspected to have Guillain-Barré syndrome. Adrenocorticosteroids therapy was started, but he became dyspneic because of the progression of paralysis to the level of respiratory muscle. He was, therefore, transferred to our emergency center on May 22, 1981.

TABLE 1. Laboratory data on admission

C B C		**Arterial blood gas**	
WCE	12800/μl	pH	7.22
RBC	$528\times10^4/\mu$l	Pco_2	21.0 mmHg
Hb	12.5 g/dl	Po_2	93.6 mmHg
Ht	38.6 %	BE	-17.0 mEq/l
MCV	73 μm		
MCH	23.7 pg	**Urinalysis**	
MCHC	32.2 %	pH	6.0
Retic.	1.0 %	protein	(−)
platelet	$19\times10^4/\mu$l	glucose	(−)
		amino acid	(−)
Mineral		ketone bodies	(−)
Na	140 mEq/l	occult blood	(−)
K	1.7 mEq/l	specific gravity	1011
Cl	116 mEq/l		
P	0.6 mEq/l	**Lumber puncture**	
Ca	4.5 mEq/l	initial pressure	150 mmH_2O
		color	xanthochromia
E K G		cell count	6/3
LVHV, U wave		protein	84 mg/dl
		glucose	96 mg/dl
Chest X-P			
CTR 60 %			

TABLE 2. Subsidiary Laboratory data

Blood Chemistry	
S.P.	8.6 g/dl
Bil	1.0 mg/dl
Al-P	79 IU/l
ADH	134 IU/l
Alb	4.5 g/dl
Glb	4.1 g/dl
ChE	218 IU/l
GOT	29 IU/l
GPT	21 IU/l
Crn	1.6 mg/dl
BUN	26 mg/dl
Amyl	332 IU/l
CPK	664 IU/l
CRP	(−)
RA	(−)
ASO	(−)

thyroid function
immunoglobulin fraction
urinary 17OHCS, 17KS
serum aldosterone
nerve conduction velocity
within normal range

β_2-microglobulin (urine) $5.7\times10^4/\mu l$
pyelography : left ureterolithiasis(+)
ICG 11 %
serum iron 75 μg/ml
TIBC 220 μg/ml

Physical examination revealed an apparently well patient without acute distress lying on bed. The blood pressure was 160/90 mmHg, and the pulse rate 90, with regular rhythm. The respiration rate was 30, and diaphragmatic in type. Neither anemia nor jaundice was evident. The abdomen was not distended, but the bowel sounds were decreased. Hepatosplenomegaly was absent. Neurologic examination disclosed that his extremities and neck were flaccid and paralytic. Cranial nerves were intact and the sensory disturbance was not demonstrable.

Principal laboratory data on admission are as shown in Table 1. Marked hypopotassemia, hyperchloremia and metabolic acidosis were found. Subsidiary laboratory data are listed in Table 2. Plain antero-posterior X-ray films of the abdomen showed paralytic ileus (Figure 1).

Checking by close observation on his respiration, 100 to 200 mEq of potassium were given by drip infusion every day. On the sixth hospital day (May 27), concentration of potassium in red cells as well as in serum returned to the normal range, and in parallel with the improvement of potassium concentration his hand grip and activity of daily life showed dramatical amelioration (Figure 2).

Chemical analysis and hemoglobin study including biosynthesis of hemoglobin in reticulocytes were undertaken in order to know which one of iron deficiency and thalassemia was the cause of his microcytic hypochromic anemia (Figure 3). The result was Hb A_2 3.45%, Hb S ($\alpha_2^A\beta_2^S$) 27.2% and Hb A($\alpha_2^A\beta_2^A$) 69.35% (Figure 4). Hb F and Hb A_{IC} were 0.17% and 4.9% respectively. These were suggestive of the sickle cell disease. The presence of Hb A as major fraction of hemoglobin in conjuction with Hb S as minor fraction is consistent with sickle cell trait (Hb S/A). Hemoglobin biosynthesis disclosed that $(\beta^A+\beta^S)/\alpha_A$ synthetic ratio was 1.4 (Figure 5). This implies that the production of α^A chain was suppressed below the level of the generation of β chains which include

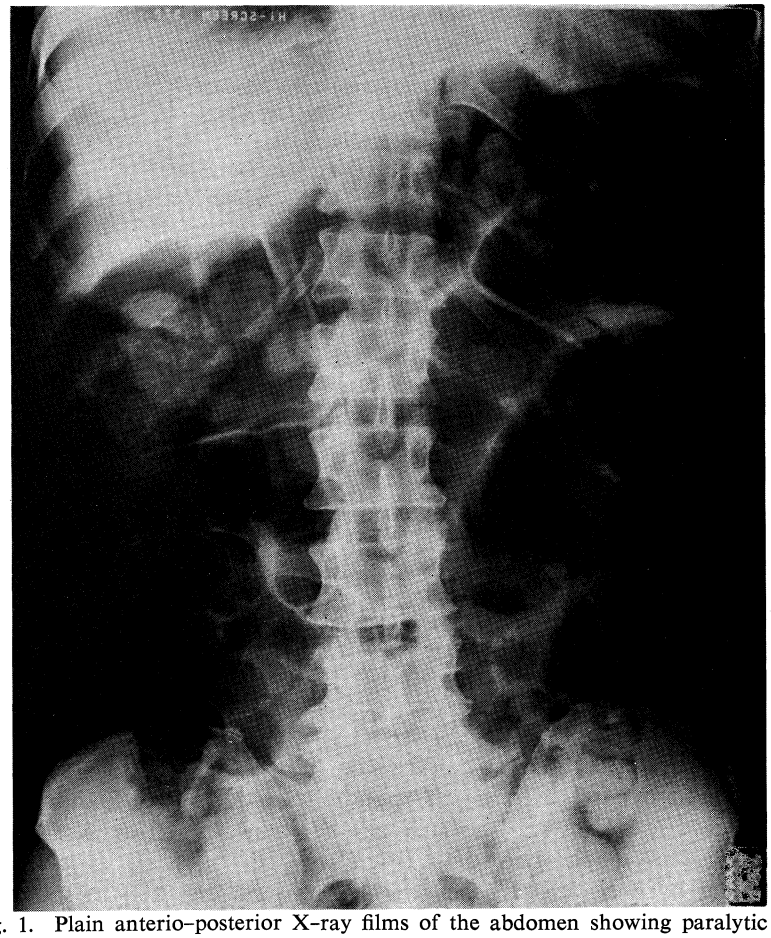

Fig. 1. Plain anterio-posterior X-ray films of the abdomen showing paralytic ileus.

normal β^A chain of Hb A ($\alpha_2^A\beta_2^A$) and abnormal β^S chains of Hb S ($\alpha_2^A\beta_2^S$). α-Thalassemia was, therefore, conceivable.

DISCUSSION

Appearance of quadriplegia associated with hypopotassemia is expected from the standpoint of motor paralysis in the following three conditions, namely, myasthenia gravis, periodic paralysis and Guillain-Barré syndrome. On the other hand, single occurrence of hypopotassemia is suggestive of primary aldosteronism, periodic paralysis, renal tubular acidosis (RTA), Cushing syndrome, Bartter syndrome and poisoning of some drugs such as licorice. Serum aldosterone, urinary 17-OHCS and 17-KS were within the normal range (Table 2). Thyroid function was also normal (Table 2). These laboratory data together

with the presence of metabolic acidosis (Table 1) were suggestive of RTA. Lowered threshold of bicarbonate secretion from the kidney is pathognomonic of proximal RTA, and the suppressed urine acidification is reminiscent of distal RTA. Distal RTA was conceivable from the absence of aminoaciduria and of glycosuria.[1,2] To confirm the possibility of distal RTA NH_4Cl (7.0g) acid-loading

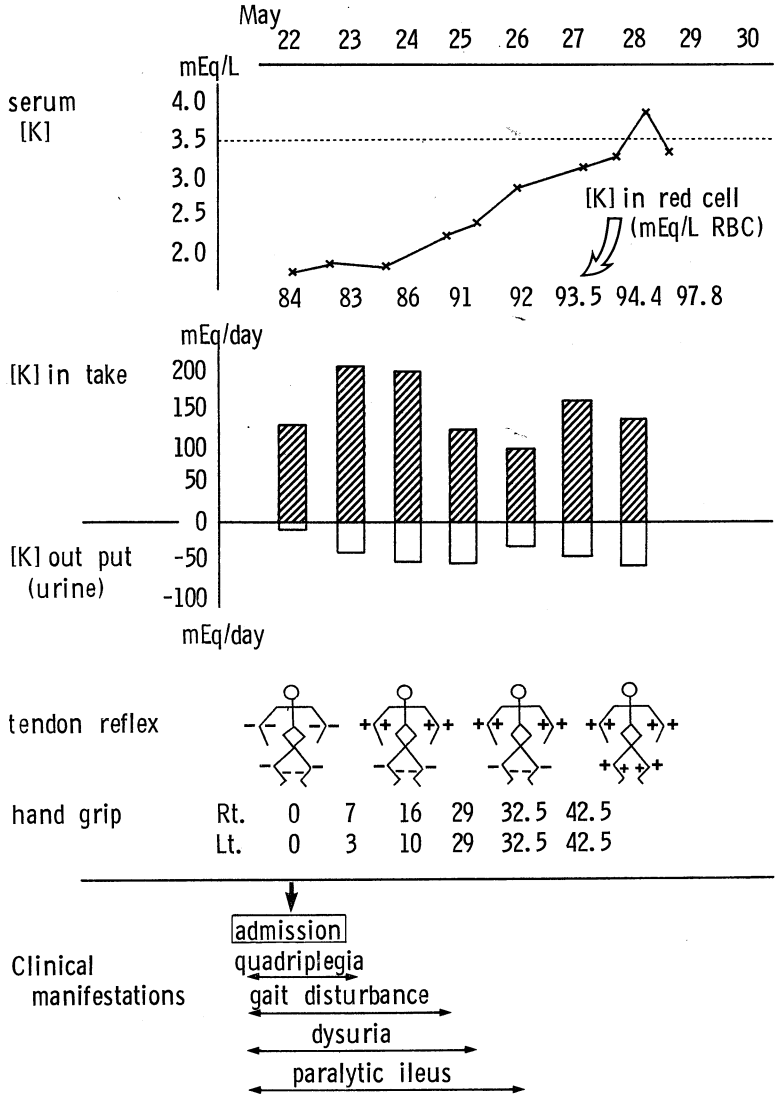

Fig. 2. Dramatical improvement of potassium concentration in serum and in red cells by intravenous administration of potassium. Restoration of normal range of potassium concentration was accompanied by neurological amelioration.

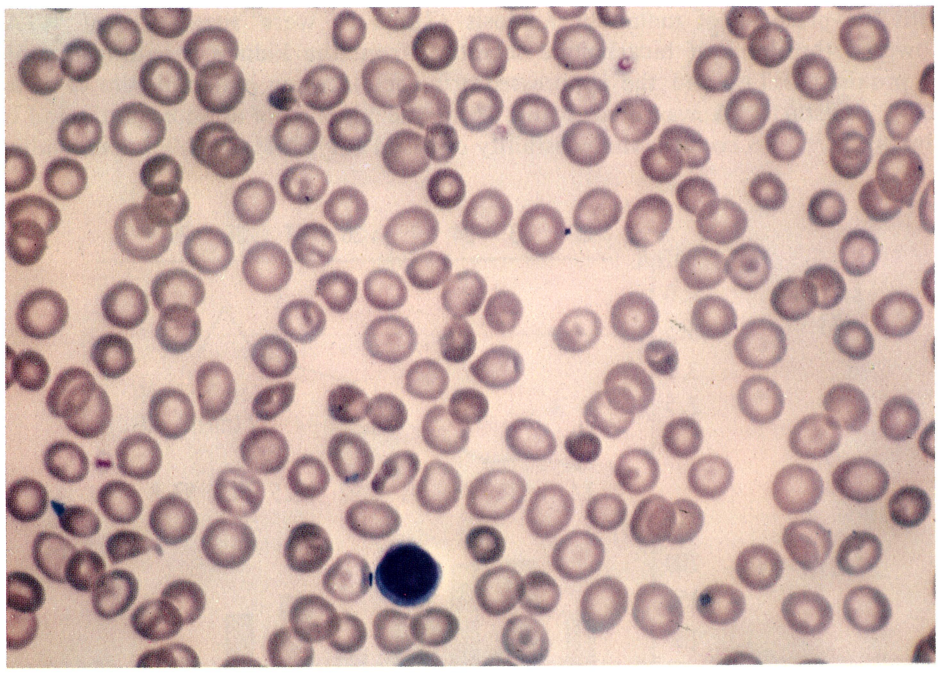

Fig. 3. Peripheral blood smears. Microcytic hypochromic red cells, target cells and spherocytes are demonstrable.

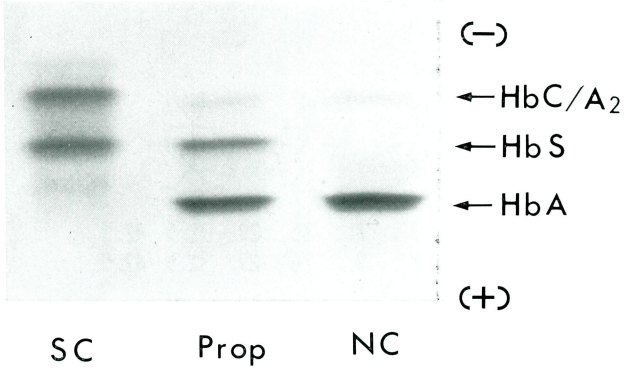

Fig. 4. Isoelectric focusing (pH range 6–9) of hemolysates. SC : hemolysate of the carrier of Hb S/C. Prop : patient. NC : normal control.

test[3] was carried out. By this test absence of the fall of urinary pH below 5.3 after having given NH_4Cl connotes the disturbance of distal renal tubules. In our patient the urine pH was 7.52 before acid-loading and remained 7.38, 7.20, 7.12, 7.10, 7.02, 7.14 and 7.08, respectively, 2, 3, 4, 5, 6, 7 and 8 hours

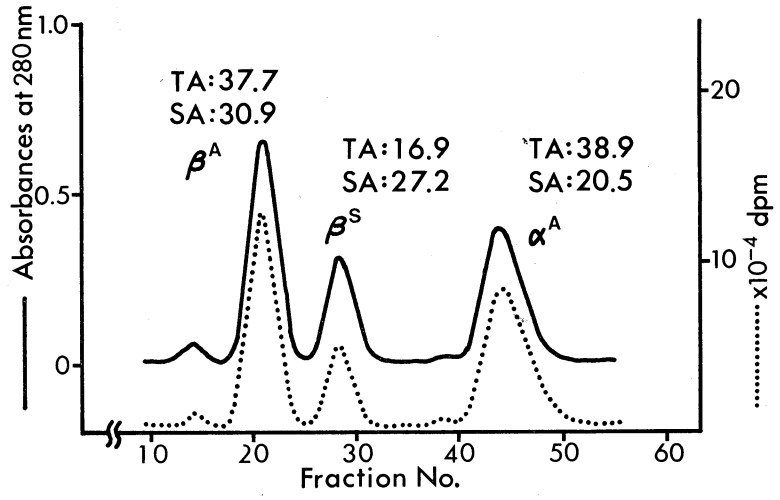

Fig. 5. Urea CM-cellulose chromatography of globin chains (β^A, β^S and α^A) obtained from biosynthesized hemoglobin, and total (TA$\times 10^{-4}$) and specific (SA$\times 10^{-4}$) radioactivities of the respective chains.

subsequent to NH_4Cl administration. The diagnosis of distal RTA is, therefore, warranted.

Guillain-Barré syndrome was also suspected from the findings of lumbar puncutre on admission, which disclosed slight pleocytosis (cell count 6/3 /μml) and increase in protein content (84 mg/dl), as shown in Table 2. However, another spinal puncture on the sixth hospital day (May 27) gave a clear cerebrospinal fluid with normal protein concentration. Quadriplegia improved in parallel with the accomplishment of the treatment for hypopotassemia and metabolic acidosis. Guillain-Barré syndrome was, accordingly, ruled out.

The microcytic hypochromic anemia with a considerably large number of target cells in his peripheral blood smears was suspicious of thalassemia, and this suspicion was affirmed positively by the increased $(\beta^A+\beta^S)/\alpha^A$ globin production ratio (1.4), which signified the presence of α-thalassemia gene. In addition the patient had Hb S and Hb A together in his blood. It was, accordingly, diagnosed that he was Hb S trait-α-thalassmia trait.

α-Thalassemia is prevalent in Southeast Asia and Jamaica.[4] It is considered that α-thalassemia, when it is associated with sickle cell anemia, inhibits in vivo sickling because it causes reduced mean corpuscular hemoglobin (Hb S) concentration, and increased intraerythrocytic Hb F concentration.[5] Higgs et al.[6] described the clinically characteristic features of the patients of α-thalassemia (homozygous and heterozygous) associated with sickle cell disease (Hb S/S). According to their observation the red cell count of the α-thalassemia (homozygous)-Hb S/S subjects was significantly above the level of the sickle cell anemia patients without α-thalassemia gene (Hb S/S), and the Hb A_2 content of

the hemolysate was also slightly higher in the patients with α-thalassemia gene than in those without α-thalassemia. There was a tendency toward lowering of Hb F content in α-thalassemia (homozygous)-Hb S/S patients. Reticulocyte counts and serum total bilirubin levels of α-thalassemia (homozygous)-Hb S/S patients were nearly normal. Mean corpuscular volume and mean corpuscular hemoglobin were low. Fewer patients (homozygous αTh-Hb S/S) had episodes of acute chest syndrome and chronic leg ulceration.

Huisman[7] noticed that there was direct (parallel) correlation of Hb S content of blood with mean corpuscular volume in α-thalassemia-sickle cell anemia ($\alpha-/\alpha\alpha$, Hb S/S). Steinberg et al.[8] laid stress on the low mean corpuscular hemoglobin and microcytosis as a striking feature of α-thalassemia-Hb S disease.

Depression of renal tubular acidification is encountered in 30%[9]-92%[10] of sickle cell anemia (Hb S/S), because the insufficiency of renal medullary blood circulation which is seen in this disease disturbs the function of the epithelial cells of the distal renal tubules. Incomplete distal RTA, which avoids metabolic acidosis,[10] is its sequel. Oster[9] and Goossens,[10] stated that there was no abnormality of acid-loading test in sickle cell trait (Hb S/A). According to Van Eps, et al.[11] renal concentrating capacity declines with increase in age and bilateral kidneys are affected equally in sickle cell trait.

The finding of our patient are somewhat different from those reported by the previous authors[9,10] which have been cited above by the presence of metabolic acidosis and abnormalities in acid-loading test. Inceased β_2-microglobulin in the urine (Table 2) may also reflect the damage of renal tubules, the cause of which has not been settled. It is, therefore, thought that our patient had secondary distal RTA in addition to the principal disease of Hb S trait-α-thalassemia trait.

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