FABRY'S DISEASE WITH RENAL TUBULAR ACIDOSIS

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Fabry's disease (angiokeratoma corporis diffusum), originally considered a dermatological disorder, is now recognized as a sex-linked systemic lipidosis in which deposits of glycolipids occur primarily in renal glomeruli and tubules and in blood vessels throughout the body. Since the original description of the condition in 1898, approximately one hundred cases have been reported. Most of the cases reported have occurred in Caucasians of European extraction. Latin American, Egyptian, and Oriental (Chinese) patients have been reported (2).

The disease is recognized by characteristic punctate, dark red skin lesion usually making its appearance in late childhood on the lower trunk and thighs. This may be associated with unexplained attacks of pyrexia and limb pains, dependent oedema, defective sweating, corneal opacities on slit lamp examination, paraesthesia of the hands and feet, proteinuria, hyposthenuria and foam cells and lipid globules in urine. Several patients have chronic bronchitis. About one quarter of them have varicose veins. Death most often results from uraemia or vascular disease of the heart or brain between the ages of 40 and 50. The full syndrome is seen in affected males (hemizygous). Heterozygous females, who may exhibit the disease in attenuated form, are most likely to show the corneal opacities.

The specific biochemical defect in Fabry's disease is unknown. It is presumed that an enzymatic defect, genetically determined, is responsible for accumulation in large quantity of products of normal intermediary metabolism.

The present report describes this rare condition in a Chinese presenting atypically with periodic paralysis due apparently to secondary renal tubular acidosis. This is the first case of Fabry's disease to be reported in Singapore and Malaysia.

CASE REPORT

In August 1966, a 34-year-old grocery assistant was admitted to Tan Tock Seng Hospital

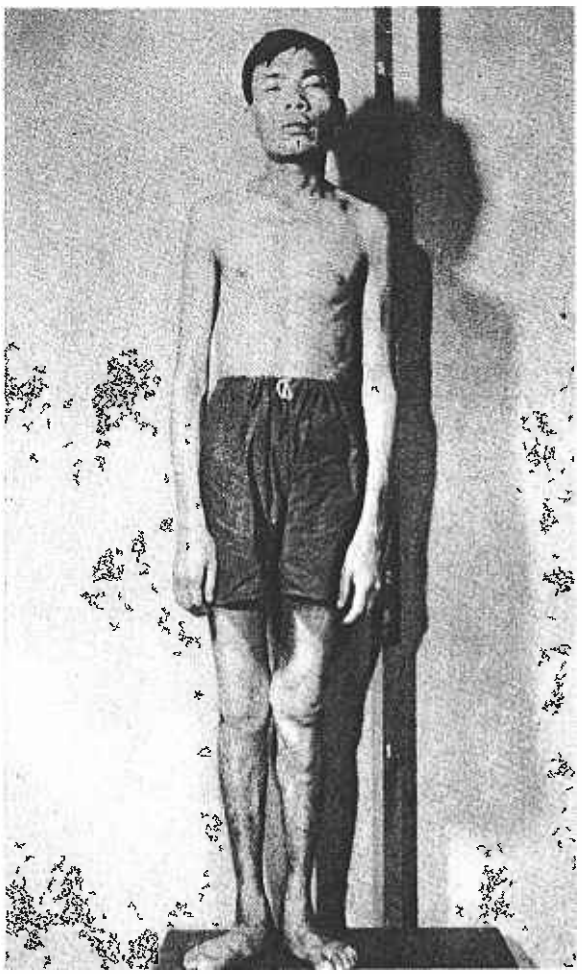
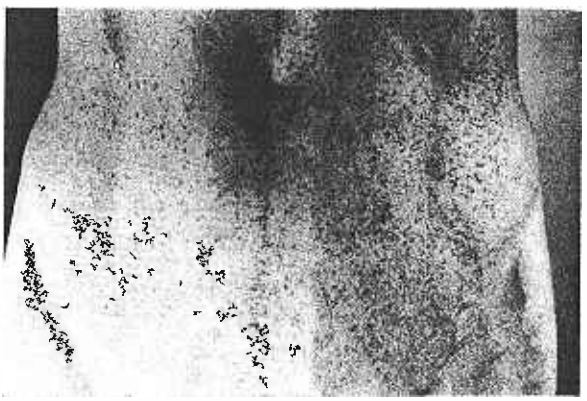


Fig. 1.



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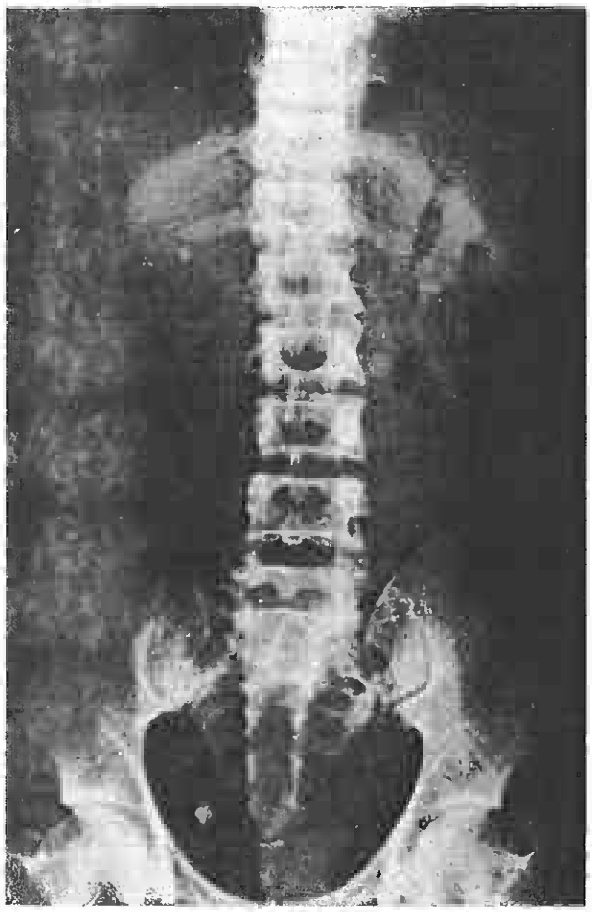

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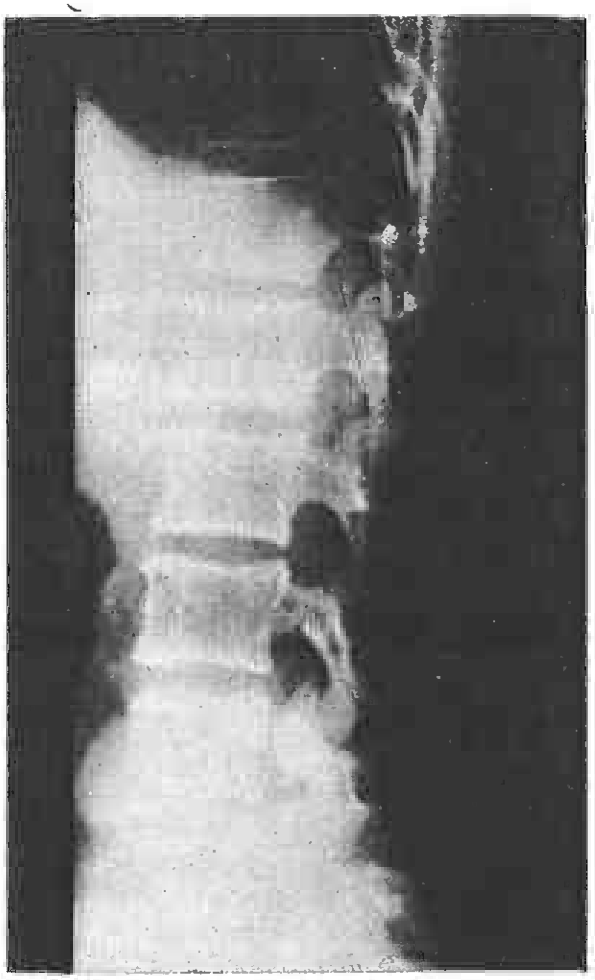

Fig. 4.

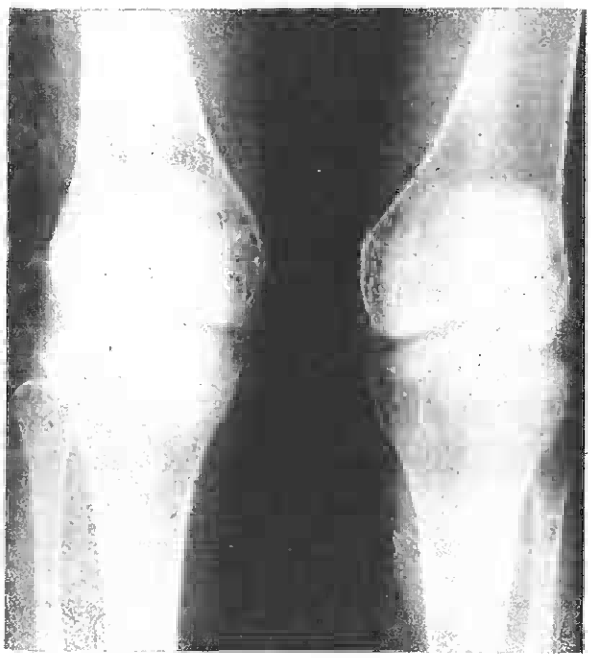

Fig. 5.

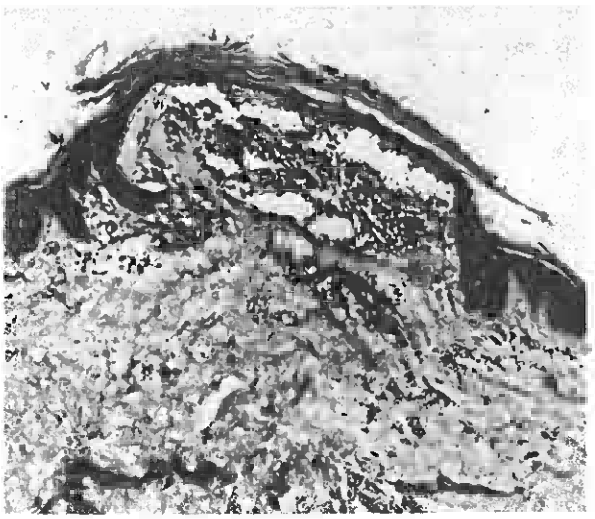

Fig. 6.

for investigation of peri odic paralysis. He had had about a dozen attacks during the preceding 8 years—each episode causing paralysis of the limbs and trunk associated with difficulty in speech, chewing and swallowing and improving after 2 to 3 days' bed rest. In addition, he had been experiencing backache, shortness of breath on exertion, intermittent swelling of ankles and thirst with nocturia for the same duration. Since the age of 6, small red spots had been present around the umbilicus and had increased gradually in number to involve the lower abdomen and lips. During childhood he had suffered frequently from fever with bodyache.

There had never been any bleeding. He does not smoke cigarettes or consume alcohol, and is single. He left China at the age of 17. The father is alive and well at 74. His mother died at 60 of "asthma". One brother aged 38 and four sisters ages ranging from 36 to 48 are well. No one in the family has reddish spots.

On physical examination he was a man of slight build (Fig. 1) of normal intelligence and fair nutritional status. The blood pressure was 100/60 and no oedema was noticed. Over the anterior abdominal wall (Fig. 2), scrotum and dorsum of the penis numerous dark-red pinpoint to pinhead-sized spots could be seen. A few lesions were present on the lips at the mucocutaneous junction. These spots tended to be grouped symmetrically on the two sides of the body and some of them could be blanched with a fine point. No lesions were seen on the face, scalp, ear or dorsum of tongue. Varicose veins were prominent especially below the left knee The fundi were normal. Visual acuity was 6/6 in both eyes. Slit-lamp examination revealed mustard coloured dystrophic changes in both cornea. Lymph nodes were not enlarged. Heart and lungs were normal. The spleen, liver and kidneys were not palpable. Neurological examination revealed that the limbs were hypotonic with muscle power ranging from grade 3 to grade 4 on admission but returning subsequently to normal. Reflexes were weak but equal. Sensory loss was not observed. Cranial nerves were apparently intact. There was no deformity or tenderness over the spine. The joints were normal except for limitation of extension at the distal interphalangeal joints of the fingers by about 20°.

Urinalysis revealed persistently low specific gravity maximal concentration 1·007 after water deprivation and pitressin administration, with protein of 200 mgm/litre (Esbach's). Microscopic examination failed to show evidence of foam cells in the urine. The serum cholesterol and electrophoresis of proteins were normal. The blood picture was normal. Urine culture grew E. coli. Following oral administration of ammonium chloride (0.1G/kg. body wt.) the PH of the urine was 6·3 four hours later (normal PH 4·6-5·2, two to four hours after dose). Additional data are presented in Table.

Chest radiograph and electrocardiogram were normal. Radiograph of abdomen showed nephrocalcinosis bilaterally with a right ureteric stone (Fig. 3). I.V.P. demonstrated kidneys of normal size and function but calcifications were noted in the renal paillae with calculi at the lower end of the right ureter. The spine (Fig. 4) showed generalized osteoporosis with thinning of cortices of long bones (Fig. 5) on radiography.

The following biopsies were performed:— Skin (from thorax): A section (Fig. 6) stained with haemotoxylin and eosin, showing mild

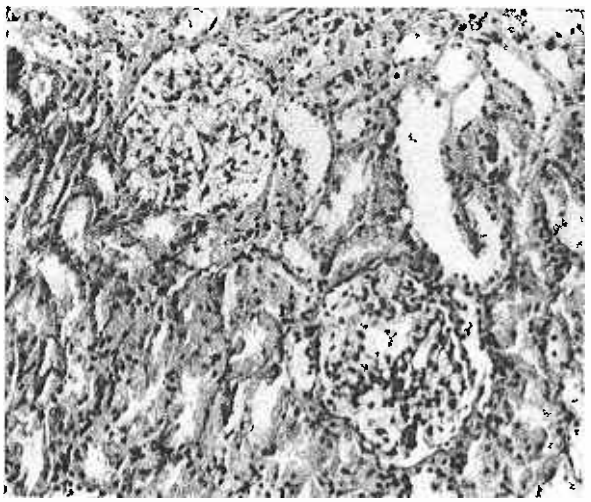

Fig. 7.

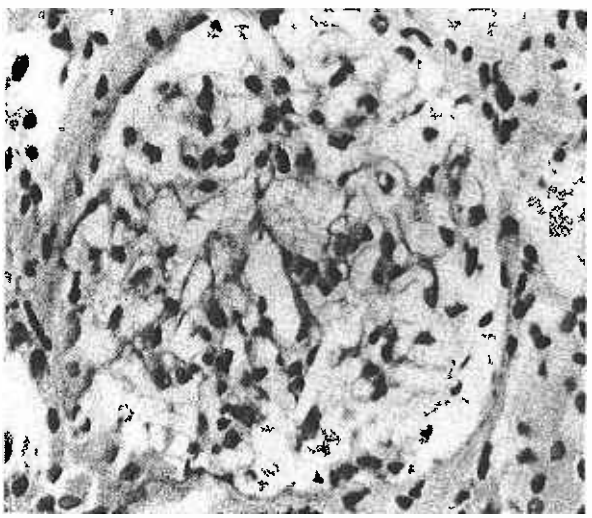

Fig. 8.

hyperkeratosis and a dilated blood-containing space in the upper corium with intact endothelial lining.

Section of Kidney stained with haemotoxylin and eosin (Fig. 7 × 150; Fig. 8 × 500), showing dilated capillary tufts with appearance of uniform vacuolation. Occasional vacuolation of epithelial cells of distal tubules seen.

ADDITIONAL DATA OBTAINED ON ADMISSION

Blood urea mg./100 ml		30
Creatinine clearance	ml/min	52·6
Serum electrolytes	mEq/L	
	Potassium	2·8
	Sodium	129
	Chloride	115
Serum alkaline phosphatase	K-A units	21·3
Serum calcium	mg./100 ml	7·8
Serum phosphate	mg./100 ml	2·6
Blood PH	=	7·27
PCO2 mm Hg	=	37
Standard bicarbonate	mEq/L =	17·1
Urinary volume ml/24 hours	=	2130
Urinary electrolytes/24 hours		
Calcium	mg.	64
phosphorus	mg.	552
potassium	mEq	44
sodium	mEq	25

DISCUSSION

The case reported here illustrates most of the features of Fabry's Disease. The characteristic skin rash, corneal dystrophy, varicose veins, oedema of ankles and arthropathy of distal interphalangeal joints of fingers (3) are encountered in the condition. Skin biopsy showing dilated capillaries and renal biopsy demonstrating vacuolated glomerular epithelial cells and vacuolated distal tubular epithelium confirm the diagnosis. Lipid deposits in kidney tissue can be demonstrated by fat stains or as doubly refractile crystals in polarized light. Routine biochemical investigations are of no value in diagnosis.

This patient had in addition features resembling those characterizing renal tubular acidosis. In the presence of systemic acidosis the urine was alkaline, indicating severe impairment of the normal mechanism of urinary excretion of hydrogen ions. Potassium excretion into the urine continued at normal rate in spite of low serum level. The urine flow was copious. Urinary concentration was not improved after water deprivation and pitressin administration. The inability to conserve water was probably a result of both nephrocalcinosis and potassium deficiency. However polyuria and a pitressin—resistent diabetes insipidus-like syndrome occasionally develops (2) in Fabry's disease. Generalized skeletal demineralization with low levels of serum calcium and phosphorus and with raised serum alkaline phosphatase indicated osteomalacia which could account for backache in this patient. A striking feature of the present case is bilateral nephrocalcinosis in the absence of hypercalcaemia and hypercalciuria. Albright and Reifenstein (1948) suggested that nephrocalcinosis in renal tubular acidosis was due to increased excretion of calcium as a result of acidosis. Although hypercalciuria is common in renal acidosis it is not invariably present, even in cases with nephrocalcinosis. It has been shown recently that the excretion of citrate in renal tubular acidosis is low or absent and may be an important factor in the pathogenesis of nephrocalcinosis.

Since urine is acidified in the distal tubule, damage to this portion of the nephron as seen in Fabry's disease might be expected to result in impairment of the process of urinary acidification. However Fabry's disease with secondary renal tubular acidosis has not been recognized except for the possible case described by Colley et al (1958). They found that their first case of Fabry's disease failed to increase titratable acidity or ammonium excretion with PH of urine of 5·14 following oral administration of ammonium chloride and suggested that this might indicate impaired distal tubule function. However their 38 year-old male patient was in the late stages of renal disease with moderate azotaemia and malignant hypertension at the time of study, and autopsy not long thereafter revealed extensive renal damage. Therefore one might more reasonably attribute these deficiencies to advanced renal disease than to predominently distal tubular defect. In our patient there is less severe renal damage with normal blood urea though the cretinine clearance was a little below lower limit of normality.

Several diseases have been described which include renal tubular acidosis as part of their clinical picture or which cause renal tubular acidosis (2). These secondary forms of renal tubular acidosis may be encountered in Fanconi syndrome, hyperglobulinaemia of various types

eg. multiple myeloma, lupoid hepatitis, Sjogren's syndrome and Hodgkin's disease. Renal tubular acidosis has been reported secondary to hypercalcaemia of Vit. D intoxication, galactosaemia, Wilson's disease, rare instances of chronic glomerulonephritis and possibly mercury poisoning. These conditions are not likely to be responsible for tubular acidosis in our case.

There is no effective therapy for Fabry's disease. Treatment is directed towards symptomatic relief of pain and to management of the renal disorder and complications. In the present case Shohl's solution has been given to combat acidosis, to replace serum electrolytes and probably to reduce existing nephrocalcinosis. After six months' therapy he has gained symptomatic relief though the serum electrolytes are low normal. Nephrocalcinosis has not been reduced.

Prognosis in Fabry's disease in males is poor though heterozygous females may be less severely affected. In this patient with renal tubular acidosis the additional hazard is progressive renal damage from fibrosis secondary to nephrocalcinosis and pyelonephritis.

CONCLUSION

A case of Fabry's disease is reported with features of renal tubular acidosis. It is suggested that Fabry's may be associated with secondary renal tubular acidosis.

ACKNOWLEDGEMENTS

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