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Maple Syrup Urine Disease (Branched-Chain Keto-aciduria) Variant Type Manifesting as Hyperkinetic Behaviour and Mental Retardation

Report of Two Cases

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INTRODUCTION

Menkes, Hurst and Craig (1954) described in a classical paper 4 children with progressive cerebral dysfunction of early onset and fatal termination in infancy, characterised by the passage of urine with a peculiar sweet odour, resembling maple syrup. Since then, the classical form of this disorder has been reported from most parts of the world, including India (Dastur, Manghani, Joshi and Adavi 1966). The biochemical basis of this disorder has now been established to be due to a defect in the oxidative decarboxylation of three branched-chain keto acids corresponding to the branched-chain amino acids valine, leucine and isoleucine (Menkes 1959; Mackenzie and Woolf 1959; Dancis, Levitz, Miller and Westall 1959).

Variant forms of the disorder are now being recognised. An intermittent form of Maple Syrup Urine Disease, with periodic attacks of ataxia, drowsiness and convulsions, precipitated by infections and accompanied by a transient ketoaciduria has been described (Morris, Lewis, Doolan and Harper 1961; Kiil and Rokkones 1964; Dancis, Hutzler and Rokkones 1967). More recently, Schulman, Lustberg, Kennedy, Museles and Seegmiller (1970) have reported another variant form of this disorder in which the patient had the characteristic accumulation of the branched-chain amino acids and keto acids constantly in blood and urine, which distinguishes the condition from the intermittent form of Maple Syrup Urine Disease, and yet showing a marked attenuation of the severe neurological damage found in the classical form of the disorder.

The purpose of this communication is to report 2 sibs with a non-fatal variant form of this disorder similar to the case reported by Schulman *et al.* (1970), occurring

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in a South Indian family. These sibs, born of a consanguineous marriage, presented with hyperkinetic behaviour and mental retardation. The possibility of an inherited disorder of amino-acid metabolism was considered in these patients because of associated skin and hair changes and the investigations revealed abnormalities of Maple Syrup Urine Disease.

CASE REPORTS

The 2 sibs were products of healthy, consanguineous parents. An elder sister is alive and normal mentally and physically. Two elder sibs were apparently premature and still-born. A younger sib was still-born after a full-term pregnancy. The pedigree suggested an autosomal recessive type of inheritance (Fig. 1).

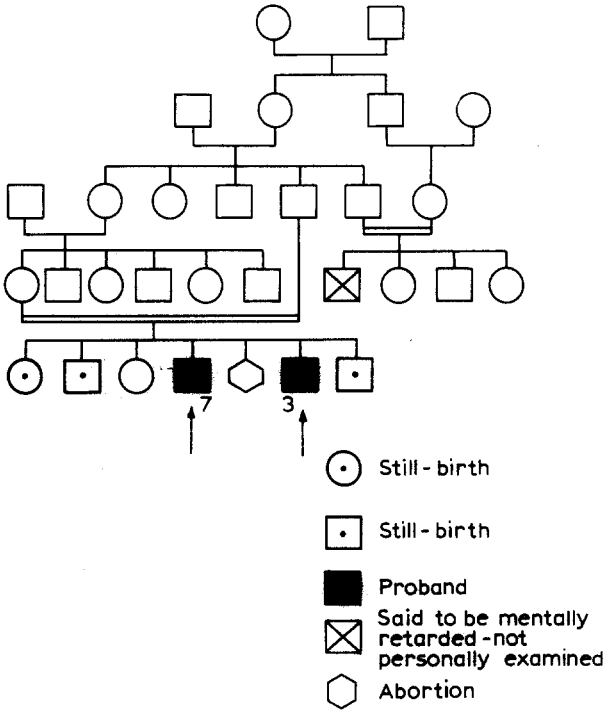

Fig. 1. Pedigree chart of sibs with Maple Syrup Urine Disease.

Case 1. Master R (N.S. No. 1297/71) was seen because of mental and motor retardation since birth. He was born after a full-term normal pregnancy and was considered to be normal at birth. According to the mother, the child suffered recurrent respiratory infections during infancy and childhood associated with a peculiar, poorly described tremulousness of the extremities. A general practitioner considered this to be incipient seizures and he was probably given anticonvulsants during these episodes. He sat at the age of 2 years and walked at the age of 3. His hair was noted to be coarse and brittle from birth. He gained toilet control at the age of 5 years. His development of speech was poor and he acquired some monosyllabic speech by the age of 5 years. Mental functions were noted to be backward. In the last 2 to 3 years before admission, in addition to being mentally retarded he had also become hyperkinetic.

On direct questioning the mother felt that the patient on occasions did pass urine with a peculiar odour, but could not recollect whether it coincided with the attacks of respiratory infections.

He was normally developed physically for his age, obviously mentally retarded, and had coarse brittle

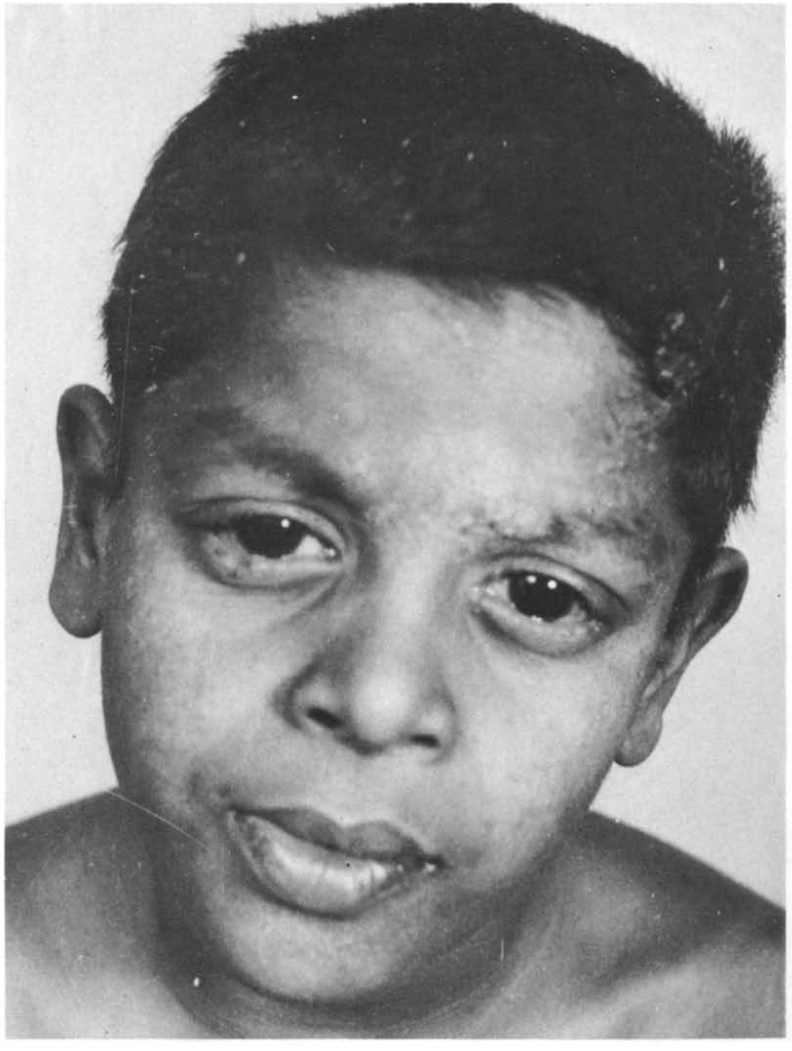

Fig. 2. Patient R, a 7-year-old boy with Maple Syrup Urine Disease showing coarse brittle hair and skin lesions of face and forehead.

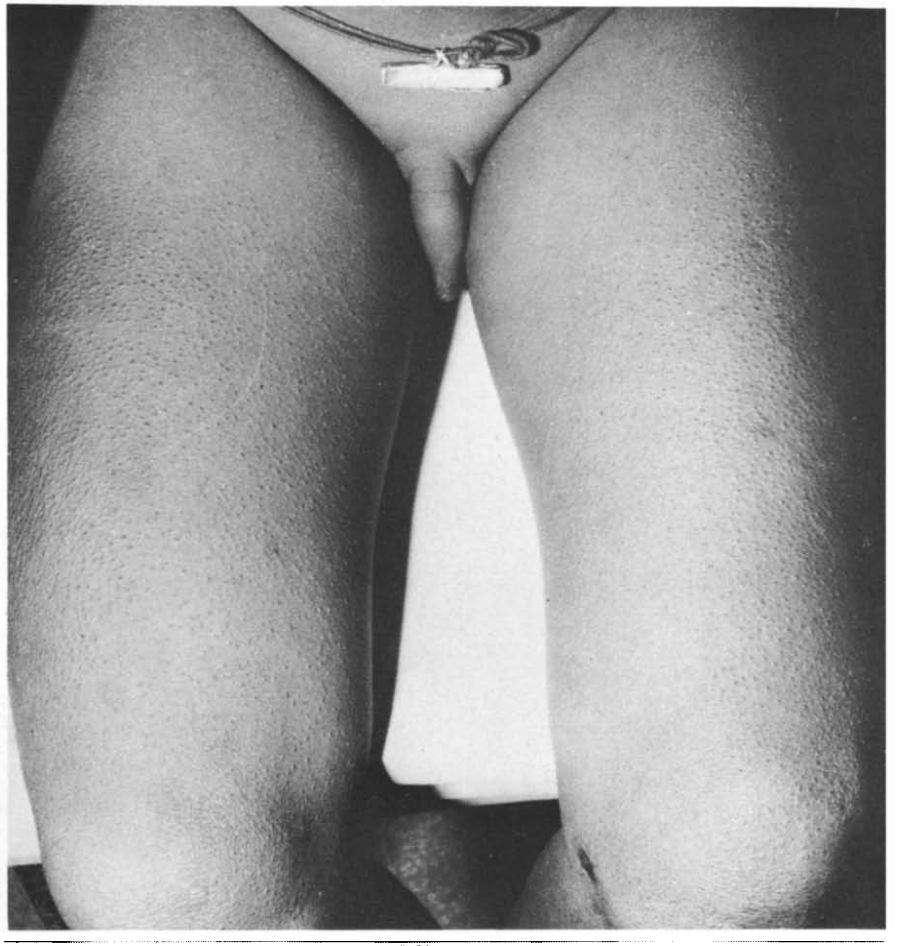

Fig. 3. Patient R showing extensive follicular hyperkeratosis of the skin.

hair and a patch of dermatitis in the middle of the forehead (Fig. 2). He was also noted to have generalised follicular hyperkeratosis of the skin (Fig. 3). He had evidence of gross vitamin A deficiency with xerosis and Bitot's spots in the conjunctivae. Examination of the cardiovascular, respiratory and gastrointestinal systems revealed nothing abnormal.

Neurological examination showed severe mental retardation (IQ 35). Speech was monosyllabic. Gait, cranial nerves, motor and sensory systems were normal. Deep reflexes were normal and symmetrical. The superficial abdominal and cremasteric reflexes were normal. Plantar responses were bilaterally flexor. There was no cerebellar or sensory incoordination. Spine was normal. Examination of the cranium showed microcephaly with a skull circumference of 19 in.

Investigations showed normal routine urinalysis, normal haemogram and normal levels of blood sugar, blood urea, serum uric acid and serum cholesterol. Total serum protein was 5.2 g/100 ml. Cerebrospinal fluid (CSF) was normal. Electroencephalogram (EEG): only sleeping record was possible and it was normal. Urine screening tests for inborn errors of metabolism showed a strongly positive reaction with dinitrophenylhydrazine, suggesting abnormal keto-aciduria. Skin biopsy: was consistent with the clinical diagnosis of follicular hyperkeratosis.

Case 2. Master V (N.S. No.1300/71), younger brother of patient R, aged 3 years was brought with the same complaints as his elder brother. He was a full-term normal child and was considered to be normal at birth. Unlike his elder brother he had not suffered from recurrent episodes of respiratory infection. He had no at-

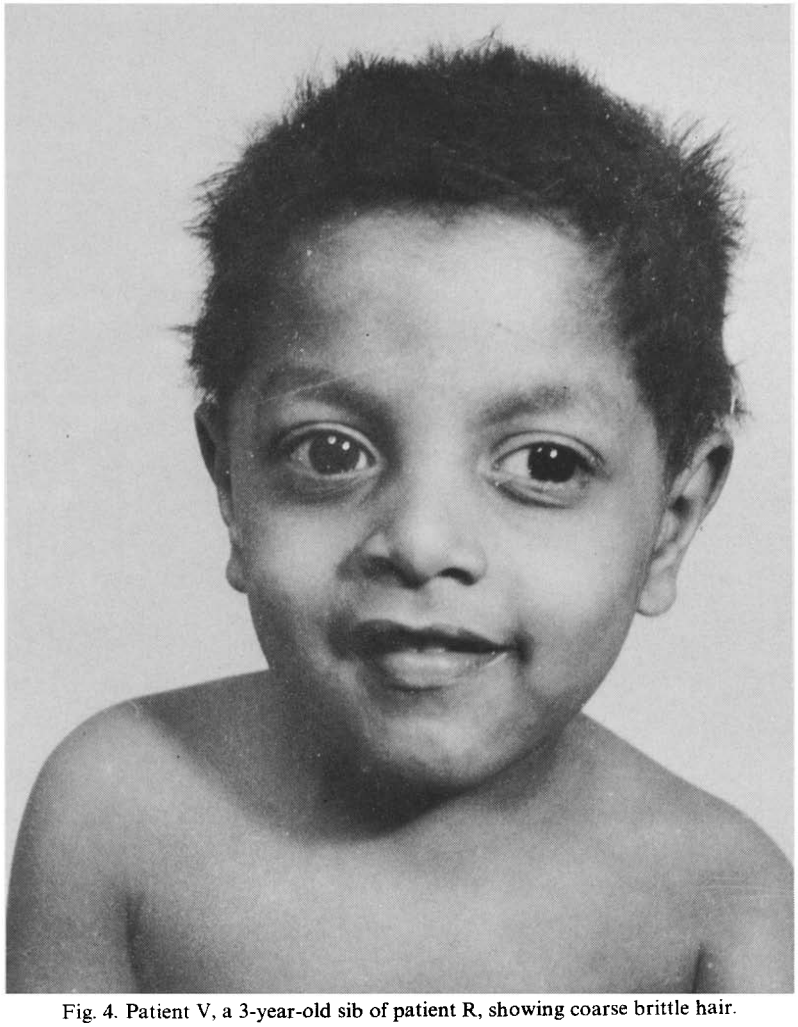

Fig. 4. Patient V, a 3-year-old sib of patient R, showing coarse brittle hair.

tacks suggestive of convulsive seizures at any time. His urine on occasions is said to have had a peculiar smell. He had been retarded from birth with delayed motor and mental milestones and had been hyperkinetic. His hair had also been noted to be coarse and brittle from birth (Fig. 4).

He was hyperkinetic, obviously mentally retarded with normal physical development for his age. He had coarse brittle hair, and follicular hyperkeratosis of skin seen on the extensor aspects of the extremities. He had no abnormality of the cardiovascular, respiratory or gastro-intestinal systems. He showed hyperkinetic behaviour, mental retardation (IQ 61) and hardly any speech development. He was microcephalic with a skull circumference of 19 in.

Investigations revealed normal routine urinalysis, normal haemogram and normal levels of blood sugar, blood urea, serum uric acid and serum cholesterol. CSF: normal. EEG: sleeping record normal. Skin biopsy: was consistent with the clinical diagnosis of follicular hyperkeratosis. Urine screening tests showed a strongly positive reaction with dinitrophenylhydrazine, suggestive of abnormal ketoacidura.

Biochemical investigations

Routine urine screening tests for inborn errors of metabolism were performed on both brothers. A dense yellow precipitate was produced with 2,4-dinitrophenylhydrazine reagent in urine from both patients suggesting the presence of excessive amounts of keto acids. Two-dimensional (ascending) chromatographic separation of the urinary amino acids on paper, using butanol : acetic acid : water (40 : 7 : 5, v/v) and phenol : water (4 : 1, v/v) systems, showed large quantities of valine and leucine in both urine samples. Chromatographic analyses of the patients' serum and CSF were also made. Quantitative estimations of the branched-chain amino acids were made by paper chromatography and elution by adopting the same technique described for phenylalanine (Varley 1967). Sera were deproteinised with 20 vols of methanol and the supernatants were evaporated to a convenient volume before chromatography. Total keto-acid content of the sera and the urines and pyruvate content of sera were determined, using the method of Friedmann and Haugen (1943). The extraction with sodium carbonate was omitted for the estimation of total keto acids. Urine keto acids were separated by paper chromatography after converting them to dinitrophenylhydrazones and extraction in xylene. The amount of keto acids was assessed visually under ultraviolet light.

The results of these biochemical investigations are given in Table 1.

TABLE 1

SERUM LEVELS OF BRANCHED-CHAIN AMINO ACIDS, KETO ACIDS, PYRUVATE AND URINE KETO ACIDS IN PATIENTS AND CONTROLS

	Amount (mg/100 ml)		
	controls (2)[a]	*patient I* (*N.S. No.* 1297/71)	*patient II* (*N.S. No.* 1300/71)
Serum leucine and isoleucine	4.0	80.3	28.5
Serum valine	3.0	18.1	15.5
Serum total ketoacids	0.81	80.0	38.4
Urine total keto acids	3.9	91.0	81.0
Serum pyruvate	0.83	0.80	0.74

[a] No. studied.

DISCUSSION

The diagnosis of Maple Syrup Urine Disease in these patients is confirmed by the abnormally high levels of branched-chain amino acids, valine, leucine and isoleucine in the serum and the markedly raised levels of keto acids in serum corresponding to these amino-acids, together with their increased excretion in urine.

It is interesting to note, however, that these 2 sibs presented with mental retardation and hyperkinetic behaviour unlike other cases previously reported. The aetiology of the hyperkinetic syndrome in childhood is ill-understood and its occurrence in sibs

is unusual (Pincus and Glaser 1966; Balasubramaniam, Kanaka and Ramamurthi 1970). The familial occurrence, the possible autosomal recessive mode of inheritance and the changes in hair which was coarse and brittle with follicular hyperkeratosis of skin suggested the possibility of an inherited disorder of amino-acid metabolism. The demonstration of either an absence or partial deficiency of the enzyme responsible for decarboxylation of the three keto acids is the specific test to establish the diagnosis of Maple Syrup Urine Disease. In the absence of facilities for such a test we have based our diagnosis on the demonstration of abnormally high levels of branched-chain amino acids and their keto acids in the serum with keto-aciduria.

Chromatographic analysis of the CSF for amino acids in our patients did not reveal any abnormality, unlike many of the previous reported cases where the CSF levels of the branched-chain amino acids were elevated (Mackenzie and Woolf 1959; Dastur *et al.* 1966). It is well-established that the concentration of amino acids in the CSF does rise with changes in blood, but only when the latter had reached a peak and is falling (Kuttner, Sims and Gordon 1961), thereby suggesting a sluggish equilibration of the brain and blood levels, unlike the case of liver and kidney. It has been shown that leucine and lysine are actively transported from the brain to the blood like many of the non-essential amino acids (Tower 1963). In the 2 cases reported here, it is possible that the concentrations of the amino acids and keto acids in the blood had not reached sufficiently high levels to accumulate in the CSF. This is probably the explanation for the lesser degree of cerebral damage in our patients compared with other classical cases who had high levels of these amino acids in the CSF.

Leucine is known to induce insulin secretion and Maple Syrup Urine Disease patients are known to have low blood glucose levels with recurrent hypoglycaemic attacks (Donnell, Lieberman, Shaw and Koch 1967). Our patients had no hypoglycaemic convulsions and their blood glucose levels were normal. The lack of hypoglycaemic attacks could also be partly responsible for the lesser degree of cerebral damage in our patients as hypoglycaemic attacks in the neonatal period can cause severe cerebral damage (Bray 1969).

Morris *et al.* (1961) in trying to explain the intermittent occurrence of symptoms with intervening normality in their patients suggested that the enzymatic defect in their cases was partial. They felt that metabolic aberrations attributable to partial deficiency may be apparent only when an unusual metabolic stress supervenes, such as that of infection. This hypothesis was later confirmed by Dancis *et al.* (1967) who studied the metabolism of leucine and valine in the leucocytes of 2 unrelated children with the variant type of the disease. The decarboxylase activity of the keto acids was greatly reduced. Although the number of determinations was small, it appeared that the reduction in enzyme activity was not as severe as in the classical forms of Maple Syrup Urine Disease, and that this accounted for the less severe nature of the disease. Even though we have not been able to study the decarboxylase activity of the leucocytes in our patients, we feel that the concept of partial deficiency of the enzyme is the most likely explanation for the longevity of our patients, as well as the absence of severe neurological deficit. Dancis *et al.* (1967) point out that patients with partial deficiency of the enzyme system are able to handle a reasonable intake of dietary

protein under normal conditions and relapse with extraordinary loads of protein such as may result from the catabolic phase associated with infections, or from a high dietary intake. Although our children were brought up as non-vegetarians, the meat intake was restricted to once or twice a week, and the children suffered from a general lack of protein as in most Indian diets. This we feel has also contributed to the longevity of our patients.

The hair and skin changes in our cases have to be explained. Although not a characteristic feature of Maple Syrup Urine Disease this may have been due to competitive inhibition between valine, leucine and isoleucine and essential nutritional factors responsible for the integrity of skin and hair. This hypothesis is supported by the suggestion of Udenfriend (1963) that in both phenylketonuria and Maple Syrup Urine Disease, phenylalanine and the branched-chain amino acids might bring about nutritional deficiencies by competitive inhibition of transport across the blood–brain barrier.

The case of Schulman *et al.* (1970) resembles our case to some extent, as their patient presented with mental retardation and was demonstrated to have an incomplete deficiency of the decarboxylase enzyme system. However, the authors did not report either hyperkinetic behaviour or skin and hair changes.

Bray (1969) has stressed the treatable nature of this condition provided the diagnosis is made early and a diet low in leucine, isoleucine and valine is started. We were certain that putting our patients on such a strict diet was unlikely to improve their mental condition. However, we decided to try them on a diet low in valine, leucine and isoleucine in the hope that the progress of the mental retardation might be arrested. We assessed the patients clinically and biochemically 6 weeks after being on this diet. The skin lesions on the face and forehead of the older boy had disappeared. Both the patients showed a remarkable reduction in the amount of keto acid in sera and urine after being on the diet for 6 weeks (Table 2). These findings clearly point to an inability to handle branched-chain amino acids.

TABLE 2

SERUM KETO ACIDS AND URINARY KETO ACIDS IN PATIENTS BEFORE AND 6 WEEKS AFTER A DIET LOW IN BRANCHED-CHAIN AMINO ACIDS

	Amount (mg/100 ml)	
	patient I (N.S. No. 1297/71)	*patient II (N.S. No. 1300/71)*
Serum total keto acids		
before treatment	80.0	38.4
after treatment	22.0	21.0
Urine total keto acids		
before treatment	91.0	81.0
after treatment	18.0	34.0

We agree with Dancis *et al.* (1967) that milder and variant forms of Maple Syrup Urine Disease may really be more common than the classical fatal form. Routine urine screening for keto-aciduria in mentally retarded children may help to detect many more cases of this type.

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SUMMARY

Two siblings with a variant type of Maple Syrup Urine Disease have been presented. They had mental retardation with hyperkinetic behaviour and skin and hair changes. They partially resemble the variant of Maple Syrup Urine Disease recently reported by Schulman *et al.* (1970). The inheritance was compatible with an autosomal recessive mode. The atypical features in our cases have been stressed. It is postulated that a partial deficiency of the enzyme system responsible for the decarboxylation of keto acids and chronic low dietary intake of protein could explain the longevity of our patients. A plea has been made for recognition of milder and variant forms of the disease, probably quite common, by appropriate investigations of mentally deficient children.

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