Family with intermittent maple syrup urine disease

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Valman, H. B., Patrick, A. D., Seakins, J. W. T., Platt, J. W., and Gompertz, D. (1973). *Archives of Disease in Childhood*, 48, 225. **Family with intermittent maple syrup urine disease.** A family is described in which the 3 children presented with episodes of severe metabolic acidosis secondary to minor infections. 2 of them died, and 1 of these was severely retarded. The sole surviving child is 6 years old and is normal with respect to physical and mental development.

Gas chromatography of the urine obtained during episodes of ketoacidosis showed the keto and hydroxy acids characteristic of maple syrup urine disease, and thin layer chromatography of the plasma and urine showed greatly increased concentrations of the branched chain amino acids. The urine and plasma of the surviving child was chromatographically normal between episodes. The leucocyte branched chain keto acid decarboxylase activity in this patient and her father was reduced.

The range of features in this family with intermittent maple syrup urine disease illustrates the necessity for prompt and careful investigation of metabolic acidosis of unknown aetiology.

Intermittent maple syrup urine disease usually presents as an attack of inappropriately severe metabolic acidosis related to trivial infections which may be followed rapidly by convulsions, coma, and death (see review, Dancis, 1967). Often the patient has been admitted to hospital on several occasions before the diagnosis has been considered, and frequently a sib has died or was mentally retarded. As the initial symptoms may occur as late as the eighth year of life (Kiil and Rokkones, 1964) and the urine and plasma are normal between attacks of acidosis, the diagnosis is easily missed. 9 families with this disease have been reported from Western Europe and America (Boisse *et al.*, 1971; Horst and Wadman, 1971; Snyderman, 1972), and we are describing a new family to show the difficulties in clinical diagnosis and the need for urgent investigation of the cause of a severe metabolic acidosis.

Case reports

The 3 children were of nonrelated, healthy parents from an agricultural area in the northwest of England. The clinical histories are reported in the order in which they presented. They were first admitted under the

care of one of us (J.W.P.). Case 1 died in 1969, and the possibility of an agricultural poison being the cause of death was carefully investigated. The other 2 children were both admitted in 1971 and, after the death of the second child, further biochemical and clinical investigations were performed at the Royal Postgraduate Medical School and The Hospital for Sick Children.

Case 1. She was born in 1967 by normal delivery after a normal pregnancy, birthweight 3.6 kg. At 19 months of age she was admitted to hospital in coma, having had a history of cough for 5 days and profuse vomiting for 2 days. She had not yet started to sit unsupported. The blood urea was 55 mg/100 ml, and the plasma potassium level 2.2 mEq/l. She received i.v. fluids, and 5 days later became fully conscious. 2 weeks later she was readmitted moribund. She had vomited persistently from soon after the time of her discharge, and was drowsy on the day before admission. She was deeply unconscious and severely dehydrated. The blood urea was 60 mg/100 ml and plasma potassium level 1.8 mEq/l. She died 24 hours later and necropsy examination, including histology of the brain, heart, and kidneys, showed no abnormalities.

Case 2. He was born in 1970 after a normal pregnancy by normal delivery, birthweight 4.0 kg. He was first admitted at the age of 10 months, with a 4-day history of vomiting. He had a right acute otitis media,

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but no gross dehydration. In addition, he was hypotonic and unable to sit unsupported. The plasma standard bicarbonate was 8 mEq/l. and the arterial blood pH 7.1. Plasma sodium level was 123 mEq/l., plasma potassium 3.3 mEq/l., blood urea 37 mg/100 ml. He received i.v. fluids including bicarbonate, and his blood pH returned to normal after 5 days of this therapy.

He was readmitted 9 weeks later with irritability but no vomiting. The blood CO₂ capacity was 11 mEq/l. and the electrolytes were normal. He was discharged 3 days later.

He was readmitted 2 days afterwards with recurrent momentary twitching of the limbs which had started shortly after discharge. He was semiconscious and irritable. The arterial blood pH was 7.29 and the plasma standard bicarbonate was 17.2 mEq/l. Acetone was present in the urine. Convulsive movements of the limbs continued, he became unconscious, and died 7 days later. Necropsy showed cerebral oedema but no other abnormality.

Case 3. She was born in 1966 by normal delivery after a normal pregnancy, birthweight 3.6 kg. The neonatal period was normal. She sat at 10 months, stood at 13 months, walked at 20 months, and began sentences at 30 months. Her mother noticed a curious odour in the urine and breath together with ataxia whenever she was 'teething' or had an upper respiratory tract infection. She had no other acute infections during infancy.

She started normal school when 4 years 10 months and was first admitted to hospital 3 months later having had loose stools and persistent vomiting for 3 days. She was in coma, dehydrated, and overbreathing. The plasma sodium level was 123 mEq/l., potassium 3.1 mEq/l., CO₂ 7m M/l., and blood urea 50 mg/100 ml. 5 hours after i.v. fluids, including bicarbonate, the arterial pH was still 7.11. She remained in coma for 36 hours. No exogenous toxic agents could be detected in blood urine, or gastric contents.

Six weeks later she had fever for 5 days which was accompanied by slurred speech and ataxia. She has had two further episodes of fever without other symptoms.

When assessed at the age of 5½ years she had no symptoms and no abnormal signs. Her weight was 19.5 kg (50th centile) and height 111.4 cm (more than 50th centile). There was no evidence of metabolic acidosis. Plasma electrolytes, blood urea, and serum transaminases were all normal. Psychometric assessment (Miss O. Swire) showed that she was above average intelligence, her mental age being 6.5 years.

Biochemical studies

Urine, collected during Case 2's terminal admission and from Case 3 during the attack when she was 5 years 1 month, was first investigated by a gas chromatographic screening procedure for the detection of abnormal organic acids and their

conjugates currently in use at the Hammersmith Hospital. The free volatile acids isolated from urine by steam distillation are analysed by gas chromatography on a neopentylglycol adipate-phosphoric acid column, and the methylated ether-extractable acids on a polyester column. Several abnormal peaks were detected during the analysis of these urines on both types of column. Gas chromatography, mass spectrometry, and ancillary chemical methods were used to establish the identity of these peaks, which were shown to be the branched chain α -keto acids and α -hydroxy acids that accumulate in maple syrup urine disease. Full details of this gas chromatographic screening procedure for organic acidurias and its use in the diagnosis of maple syrup urine disease are presented elsewhere (Gompertz and Draffan, 1972).

Quantitative amino acid analysis of the same urine and also a stored plasma sample showed the typical branched chain aminoaciduria and amino-acidaemia seen in maple syrup urine disease (Table I).

TABLE I
Amino acid analysis of urine and plasma

	Case 2 Terminal admission		Case 3 5 yr 1 mth
	Urine	Plasma	Urine
Valine	2.68	21.6	5.36
Alloisoleucine	0.41	3.0	0.37
Isoleucine	1.96	17.0	1.87
Leucine	4.12	66.7	4.44

Note: Results are presented as mg/100 ml; analyses were performed by ion exchange column chromatography.

When the urine of Case 3 was analysed during remission, neither gas chromatography of organic acids nor amino acid analysis revealed any abnormality. However, during this period, studies performed on leucocytes from Case 3 and her parents revealed impaired oxidative metabolism of the branch chain amino acids.

α -Ketoisocaproate dehydrogenase activity of white blood cells was estimated by a method similar to that of Dancis, Hutzler, and Rokkones (1967). The substrate was (U-¹⁴C)-L-leucine. The results (Table II) showed a marked reduction of activity in the patient's cells, and it is of some interest that the residual activity was similar to that found in a patient with acute infantile maple syrup urine disease. The number of control determinations was small but it appears reasonably certain that enzyme activity in the father of our patient was also considerably reduced.

TABLE II

α-Ketoisocaproate dehydrogenase activity of white blood cells

Subjects	¹⁴ CO ₂ released (dpm/hr per 10 ⁶ cells)
Case 3	18
Mother	43
Father	29
Controls	Range (mean)
Children (6)	109–172 (132)
Adults (4)	50–101 (74)
Acute maple syrup urine disease	22

dpm, disintegrations per minute.

Discussion

The clinical features of this family are typical of the presentation of intermittent maple syrup urine disease (Morris *et al.*, 1961; Boisse *et al.*, 1971). Episodes of severe metabolic acidosis and dehydration are often precipitated by minor upper respiratory or gastrointestinal tract infections and may be fatal within a few hours. These attacks are often associated with loose stools, but the metabolic acidosis is inappropriately severe for the duration and extent of the symptoms. Though the patient may present with mental retardation during the second year of life (Snyderman, 1972), the first symptoms may be delayed for up to 8 years and be accompanied by normal intellectual and physical development (Kiil and Rokkones, 1964). Even in the most recent reports one or more sibs have died and the patient has been readmitted on several occasions before the diagnosis has been considered (Horst and Wadman, 1971).

Severe metabolic acidosis precipitated by minor infections is a feature common to several organic acidurias: isovaleric aciduria (Tanaka *et al.*, 1966) and methylmalonic aciduria (Oberholzer *et al.*, 1967), as well as intermittent maple syrup urine disease. The organic acidurias have no specific clinical features and accurate diagnosis depends on a comprehensive screening method. Gas chromatography provides an effective screening method for maple syrup urine disease (Greer and Williams, 1967; Gompertz and Draffan, 1972) as well as other organic acidurias and acidurias (Perry *et al.*, 1970; Hammond and Goodman, 1970; Jellum, Stokke, and Eldjarn, 1971).

The recent report of the response of a patient with maple syrup urine disease to thiamine (Scriver *et al.*, 1971) shows that this disease should be grouped with other organic acidurias in which vitamin responsive variants have been described: lipoic acid in Leigh's encephalopathy (Clayton,

Dobbs, and Patrick, 1967), vitamin B₁₂ in methylmalonic aciduria (Rosenberg, Lilljeqvist, and Hsia, 1968), and biotin in propionic aciduria (Barnes *et al.*, 1970) and β-methylcrotonylglycinuria (Gompertz *et al.*, 1971). The high mortality rate in organic acidurias and the possibility of specific treatment with a vitamin or a diet suggest that screening tests should be performed urgently in a patient with metabolic acidosis of unknown aetiology.

The results of the white cell branched chain amino acid decarboxylase assay show low levels in the patient and her father, and possibly a moderately decreased level in her mother. These results are similar to those of some previous authors, though there is a considerable range in the various reports (Dancis *et al.*, 1967; Horst and Wadman, 1971). This variation may be due to different specific enzyme defects in the patients, as there may be 2 (Bowden and Connelly, 1968) or 3 different dehydrogenase enzyme complexes involved in the oxidative decarboxylation of the branched chain keto acids (Goedde *et al.*, 1970).

A few months after Case 3 returned home she had bronchopneumonia and acetone was present in her urine. She was admitted to the West Cumberland Hospital where she received a low protein diet (0.5 g/kg per day) with adequate calories supplied by carbohydrate and thiamine hydrochloride 10 mg daily. Frequent estimations of the plasma standard bicarbonate showed only a mild acid-base disturbance. She was discharged on a normal diet and her mother checks her urine for acetone with Acetest tablets daily.

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