Variant maple syrup urine disease in mother and daughter

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Summary: Intermittent MSUD in a mother and her daughter is reported. Fibroblast cultures were studied for branched-chain keto acid decarboxylase and results show that the mother has approximately 12% while the daughter has 5% of the normal enzyme activity. Other key members in the family were also studied for enzyme activity. It appears that the child has inherited an abnormal gene from her homozygous mother and another abnormal gene from her heterozygous father.

A classification based on the degree of residual enzyme activity and protein tolerance places the mother in grade III and the daughter in grade II category. Classical MSUD, where the enzyme activity is less than 2% of normal, belongs to grade I.

Résumé: *Une variante de la maladie des urines à odeur de sirop d'érable chez une mère et sa fille*

L'article rapporte un cas de syndrome de Menkes intermittent chez une mère et sa fille. Par culture de fibroblastes, on a dosé la décarboxylase des céto-acides à chaines latérales. Ces dosages ont montré que la mère présentait 12% et la fille 5% de l'activité enzymatique normale. On a également recherché l'activité enzymatique chez d'autres membres-clés de la famille. Il en ressort que l'enfant aurait hérité de sa mère homozygote un gène anormal et de son père hétérozygote un autre gène anormal.

D'après la classification basée sur l'activité enzymatique résiduelle et la tolérance protidique, la mère serait classée dans la catégorie grade III et la fille dans la catégorie grade II. Le syndrome de Menkes classique, dont l'activité enzymatique est inférieure à 2% de la normale, est considéré comme grade I.

Maple syrup urine disease (MSUD) is an inborn error of metabolism with autosomal recessive inheritance in which the enzyme defect involves the degradation of the three branched-chain amino acids, leucine, isoleucine and valine (Fig. 1). In the classical case severe neurological symptoms appear during the first weeks of life, and death follows soon after. These serious consequences can be avoided by the early institution of dietary control which prevents an increase in plasma branched-chain amino acids and keto acids to toxic levels.

The genetic defect becomes manifest acutely in early infancy and has attracted the attention primarily of pediatricians and geneticists. Variants of MSUD are now being described with increasing frequency.[1-9] In these patients there is a variable amount of residual activity of the branched-chain keto acid decarboxylase. As a result the necessary dietary restrictions are less stringent, the onset of symptoms is generally delayed and less severe, and the chances of reaching adult life are proportionately increased. In many of these patients symptoms are intermittent in character.

In the intermittent forms of MSUD clinical or biochemical abnormalities are not detectable unless the patient is under conditions of stress, such as fever or infection, causing an increased breakdown of endogenous protein, or has an excessive dietary intake of protein. At such times symptoms of anorexia, vomiting, ataxia, hypertonicity and lethargy which drifts into coma may occur. The condition either becomes irreversible and fatal within a few days or the patient recovers spontaneously or as a result of treatment, in which case neurological and intellectual functions appear to return to normal.

In the present communication we describe an adult woman (case 1) in whom the diagnosis of a mild form of MSUD (grade III) was made after delivery of a child (case 2) with a more severe form of the disease (grade II). The three types of MSUD are explained in Table I. These cases raise several questions worthy of the attention of internists and obstetricians.

Case reports

Case 1

Bo Ro is the eldest of five children ranging in age from 6 to 24 years, all developing normally. She was born in January 1948 at term with a birth weight of 3.3 kg.; labour and delivery were normal. Her development was normal but at the age of 5 years, following a protracted feverish cold, she was admitted to hospital because of fever, anorexia, vomiting and lethargy. She was treated with intravenous glucose in saline and Ringer's lactate. She was discharged after eight days with a final diagnosis of electrolyte imbalance. Apart from this episode she had no serious illness. She is 160 cm. tall, weighs 51 kg. and has above-average intelligence. Her only pregnancy was without complication, apart from five-weeks' delay in the onset of labour. She suffers from mild eczema which she attributes to food allergies. She craves candy and chocolate. She drinks two to four glasses of milk per day. She often feels weak and faint after a bigger meal and this is relieved if she takes a sweetened drink or a bar of chocolate. She feels at her best in the morning if she omits breakfast and she prefers small snacks to regular meals. She is an ambitious, tense person, very apprehensive of any medical procedures.

Case 2

Ni Ro, daughter of Bo Ro, borne November 1969,[10] is the first child of non-consanguineous parents, both 21 years of age at the child's birth and both university students. The pregnancy was uneventful but birth was four to five

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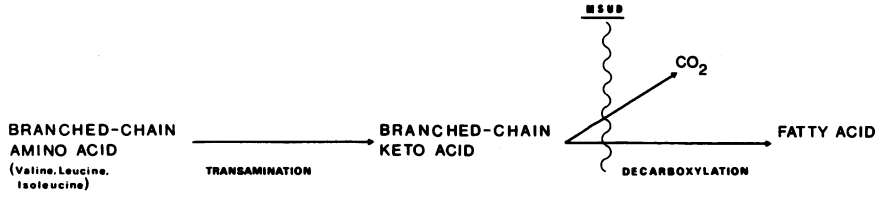

FIG. 1—Degradation of the branched-chain amino acids.

weeks beyond term. Following induction, labour and delivery were normal. The infant weighed 3.1 kg. at birth, length was 48 cm. and head circumference 32 cm. Physical development was normal apart from an equinovarus deformity of the right foot. The infant was pale and flaccid with dry, puckered skin in postmature fetal distress. Apgar rating was 8.

She was breast fed for 2½ months and then placed on Enfalac®. She developed normally and routine immunizations were without unusual reactions; she was not vaccinated against smallpox.

At eight months her diet was changed from Enfalac to cow's milk, thus doubling the protein intake from milk. She was at this time on canned baby foods, which brought the protein intake to between 4 and 5 g./kg./day. Two weeks later she became ill with otitis media and was admitted to hospital because of emesis and an unusual lethargy. She had been intermittently irritable, drowsy and anorexic for approximately 10 days prior to admission and the mother had observed that the child's body and urine had acquired a peculiar odour. Truncal ataxia was also noted on admission. During the following three days in hospital her condition continued to deteriorate. She required forceful feeding but this was frequently followed by emesis. She became more lethargic, responding with irritability when disturbed. Hypertonia and jerky movements of upper and lower extremities appeared. A persistent "sweetish, spicy" odour was noted. Although routine investigations were not helpful, biochemical studies done on the fourth day revealed elevated levels of leucine, isoleucine and valine, and their keto acids in blood and urine (Fig. 2). The child received intravenous therapy of glucose in saline and 36 hours later she became more alert. In four days the blood and urine were normal and the child appeared dramatically recovered.

Following her illness Ni Ro was placed on reduced protein, 2 g./kg./day, and on this regimen she has maintained satisfactory metabolic balance in spite of several feverish colds and anesthesia on two occasions to permit surgical correction of her right foot deformity. The mother stops all protein intake for one or two days when the child becomes feverish. An attempt to allow a free diet, using Enfalac and excluding cow's milk, resulted in a protein intake of between 3 and 4 g./kg./day, which produced a gradual rise of branched-chain amino acids in the blood (Fig. 2).

Ni Ro's psychomotor development is average for her age. At 30 months of age her height is 90 cm. (50th percentile), her weight 10.9 kg. (3rd to 10th percentile) and head circumference 46.8 cm.

A therapeutic trial of thiamine,[11] 10 mg./day for 10 weeks, did not result in increased appetite or weight gain. An attempt to increase the protein intake while on thiamine had to be discontinued when the child developed a feverish cold.

Special studies

Methods

Samples of the patients' urine were examined by the usual chemical tests for keto acids. Plasma and urinary amino acids were examined using two-dimensional paper chromatography and an amino-acid analyser.

Enzyme assays were performed on skin fibroblasts grown in tissue culture. Skin biopsies were taken from the deltoid region or the upper thigh and grown in Waymouth's medium, using conventional techniques. Fibroblasts were collected from a confluent culture and incubated in suspension with a branched-chain amino acid labelled in the carboxylcarbon. The amount of radioactive CO_2 that was liberated provided a measure of the decarboxylase activity (Fig. 1). The details of the technique have been previously described.[12,13]

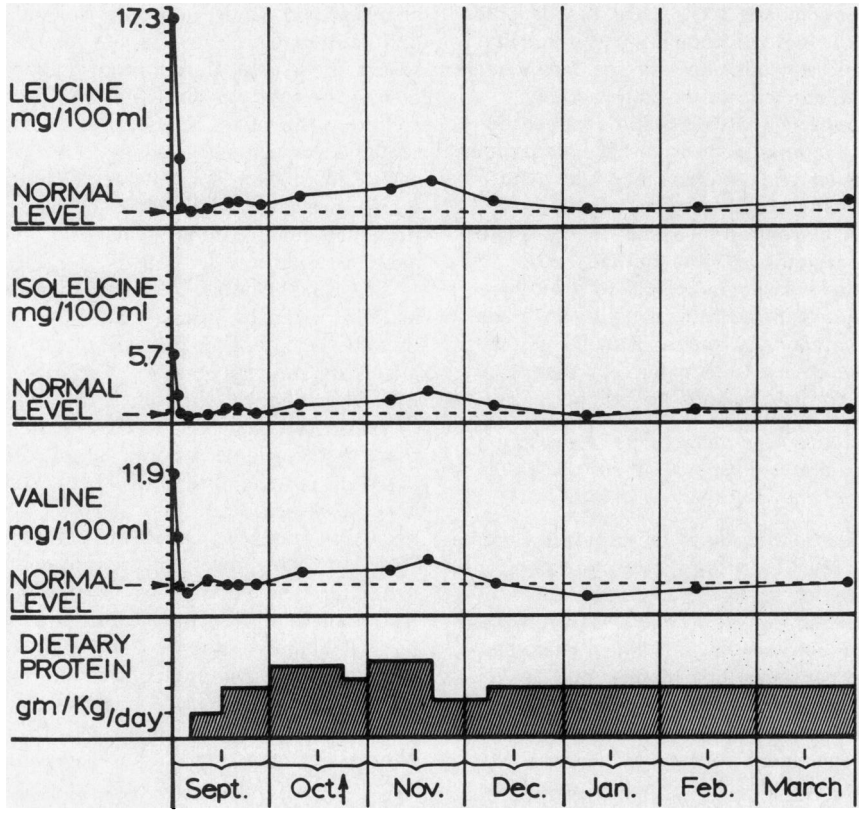

FIG. 2—Very high leucine, isoleucine and valine concentrations in the plasma during the acute stage of MSUD, rapidly returning to normal on withdrawal of protein intake, remaining at a normal level when dietary protein is restricted to 2 g./kg. body weight but rising again if protein is increased above that level.

Table I—Classification of MSUD

	Grade I (classical MSUD)	Grade II	Grade III
Enzyme level	0-2%	2-8%	Greater than 8%
Dietary protein tolerance*	Inadequate to maintain nitrogen balance	1.5-2 g./kg.	Normal or marginal decrease
Type of diet needed	A significant proportion of nitrogen is provided by purified amino acids with regulated amounts of BCAA	Low-protein diet; breast milk or equivalent proprietary milks may be tolerated but not cow's milk	Unrestricted diet
Clinical characteristics	Symptoms of classical MSUD appear in first weeks of life	Symptoms often delayed in onset and intermittent; induced by high protein intake and stress	Acute symptoms of MSUD may appear during stress, especially infections

*Protein tolerance depends on ability to degrade dietary branched-chain amino acids (BCAA).

Results

Plasma branched-chain amino acid levels in Bo Ro (case 1) were all within normal limits and those in Ni Ro (case 2) are presented in Fig. 2.

The results of the enzyme assays are summarized in Table II. The enzyme activity in Ni Ro is 5% of normal, placing her in grade II category (Table I). This group requires a limitation in dietary intake of protein to remain symptom-free. The mother, Bo Ro, is borderline grade II to grade III, particularly in respect to leucine, which is responsible for most of the toxic symptoms in maple syrup urine disease.

Discussion

A complete investigation of the family was hampered by the wide geographical dispersion of the members and by the unwillingness of some to submit to study. However, the key members were studied (Fig. 3) and certain reasonable deductions can be made.

The enzyme activities of the skin fibroblasts of the parents of Bo Ro (case 1) are within the normal range. This is consistent with our experience in classical MSUD in which we have found the heterozygote value to be lower as a group, but to overlap the normal range. The remote possibility of a mutation with a dominant mode of inheritance can be excluded because the enzyme activities of the parents were considerably higher than those of Bo Ro.

Barring the unlikely eventuality of a new mutation in Bo Ro, it must be assumed that each of her parents carries a mutant gene directing the synthesis of a branched-chain decarboxylase with reduced activity. Bo Ro inherited both mutations so that her enzyme activity is 12% of normal. This has permitted her to tolerate, without symptoms, a relatively normal protein intake except for moderate restrictions that she has consciously imposed upon herself because this makes her feel better.

However, at 5 years of age, she was admitted to hospital with anorexia, vomiting and lethargy following a simple respiratory infection. This episode is suspiciously reminiscent of those described in intermittent branched-chain ketoaciduria. Presumably, during the catabolic phase of an infection, tissue proteins rich in branched-chain amino acids may be rapidly degraded, overwhelming a limited enzyme capacity.

Ni Ro appears to have inherited a mutant gene from her apparently normal father as well as from her mother. Her enzyme activity is lower than her mother's, and symptoms became manifest at 8 months of age following dietary change from a low to a high protein milk. However, she is neurologically intact and her outlook for a normal life, with relatively minor dietary restrictions, is good.

These two patients raise important questions for internists and obstetricians. If a patient not known to have a variant form of MSUD were to develop vomiting, ataxia and coma following a relatively minor infection, the diagnosis would probably be "acute toxic encephalopathy". The routine administration of intravenous fluids might be sufficient to reverse the symptoms even if a correct diagnosis were not made. However, in the more serious case it might be necessary to use exchange transfusion and peritoneal dialysis and possibly to specifically restrict the intake of branched-chain amino acids temporarily. If an acute episode were to occur during pregnancy with elevation in the blood levels of the branched-chain amino acids and keto acids, it is quite possible that the fetus would be damaged even if it did not inherit the genetic defect. The analogous situation has been reported in phenylketonuria.

In six of the reported cases of intermittent MSUD the first symptoms developed between 9 and 17 months of life.

It is known that requirements of amino acids (per kg. body weight) which are necessary for normal growth decrease during the first 12 to 18 months of life,[14] and also that children with classical MSUD on dietary treatment have a relatively higher tolerance for branched-chain amino acids in early infancy. The same situation applies in such conditions as homocystinuria and phenylketonuria. Therefore close monitoring and adjustment of diets are necessary because a protein intake which will maintain desirable levels in the first weeks of life of the amino acid concerned will exceed the patient's tolerance a few months later. A child with intermittent MSUD may initially tolerate a protein intake similar to that of a normal infant but soon after 8 months of life his dietary protein will have to be limited if he is to remain symptom-free.

Because Bo Ro has two mutant genes

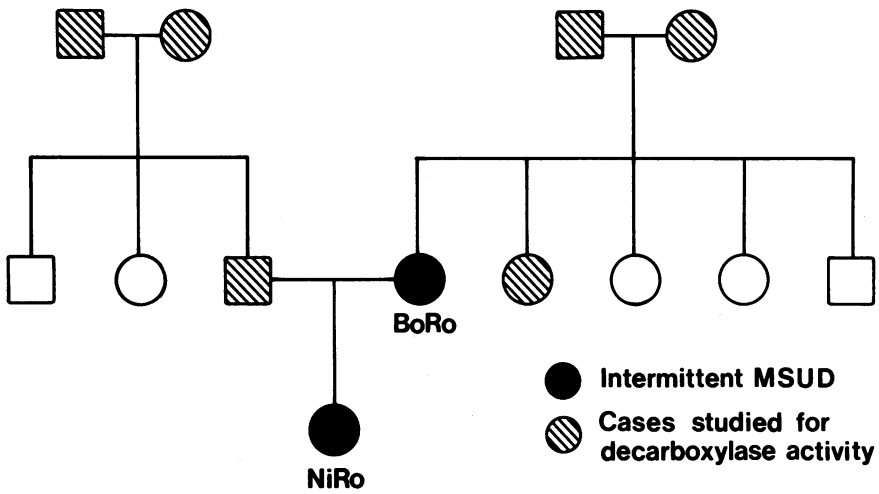

FIG. 3—Family tree indicating the position of the two cases of intermittent MSUD as well as the relatives studied for enzyme activity.

Table II—Branched-chain keto acid decarboxylase activity in fibroblast culture

	Leucine	Isoleucine	Valine
Ni Ro — propositus (case 2)	5	5	6
Bo Ro — mother (case 1)	8	18	12
Br Ro — father	107	186	126
B St — maternal grandmother	106	137	127
Go St — maternal grandfather	72	163	89

Presented as % of the mean of 22 control subjects, ranging in age from newborn to middle life; the donor's age did not significantly affect the enzyme activity. One biopsy from Ni Ro and two biopsies from Bo Ro were studied on three and five occasions respectively. The other subjects were assayed twice. Enzyme activities of mother and father of case 1 and father of case 2 fall within 25% (± 1 standard deviation) of the normal mean.

and the husband probably has one, the risk of a child being born with two mutant genes is 50%, rather than the usual 25% in recessive diseases. Furthermore, since the statistical probability is that Bo Ro has two different mutant genes, the phenotype of an affected child will be influenced by which gene is inherited from the mother. The next affected child might conceivably have significantly milder or more severe disease than Ni Ro if there is a significant disparity in the severity of the enzyme defect introduced by each of Bo Ro's genes.

When the concept of inborn errors of metabolism was first introduced into clinical medicine, there was a tendency to classify populations into three categories: the homozygote, with a severe, often total enzyme defect; the heterozygote, with enzyme activity that approximated 50% of normal; and the normal group. We now recognize that multiple mutations may involve a single gene locus and each mutation may cause a variable reduction in enzyme activity. Conceivably, some mutations produce an increase in enzyme activity. In an autosomally recessive disease the afflicted individual may inherit a different mutant gene from each parent, further increasing the variability of the effect. As a result, measurement of enzyme activity may not yield three sharply divided populations, but a distribution curve similar to the familiar ones for height and weight. The recent experience with the variant forms of MSUD suggests that this may be true for the branched-chain keto acid decarboxylase.

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