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SHORT REPORT

The longest-surviving patient with classical maple syrup urine disease

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Summary The clinical problems, dietary management and biochemical monitoring over a 40-year period of the longest-surviving patient with maple syrup urine disease are described. Her case illustrates that a good outcome can be obtained with early diagnosis and institution of a diet restricted in branched-chain amino acids. Changes in dietary supplementation have benefited her in terms of nutrition and quality of life. Consistently high blood concentrations of branched-chain amino acids have not been associated with neuropsychometric decline.

Introduction

The clinical picture of maple syrup urine disease (MSUD, McKusick 248600) is caused by the effects of toxic metabolites, especially keto-isocaproic acid, on the central nervous system. Progressive encephalopathy occurs in the first week of life. Problems with feeding, lethargy and somnolence are usually associated with cerebral oedema and consequent coma.

MSUD is inherited in an autosomal recessive fashion with an approximate incidence of 1:200 000. It is due to a defect in the branched-chain alpha ketoacid dehydrogenase enzyme complex (EC 1.2.4.4), which results in accumulation of valine, leucine, isoleucine and alloisoleucine. Urine organic acids such as branched-chain keto- and hydroxy-acids are elevated.

Acute treatment consists of detoxification by exchange transfusions and/or haemofiltration together with intravenous glucose and insulin. Protein is withdrawn from the diet and subsequent dietary intake is protein-restricted with monitoring of branched-chain amino acids (BCAAs) guiding therapeutic adjustments. Supplementation of other amino acids, vitamins and trace elements is necessary to avoid deficiency states (Chuang and Shih 2000).

The prognosis for affected children has improved dramatically, but few patients have survived into their fifth decade and thus many questions remain about the long-term outcome and whether strict adherence to diet is important. Here we report the case of the longest known survivor with neonatal-onset MSUD.

Case history

First year

A female infant was born in 1961 following a normal pregnancy. She was the third sibling of healthy unrelated parents, both of whom were manual workers. The first sibling, a baby girl, had MSUD and died at 15 months. The second sibling was unaffected. At birth, the patient described in this report was well, but she was observed closely because of the family history (Westall 1963). At birth she weighed 2.83 kg (9th centile), was 49.5 cm (25th centile) long, and had a head circumference of 34.3 cm (25th centile). She was diagnosed with MSUD on the basis of clinical symptoms and signs on day 5: lethargy, feeding difficulties and maple syrup odour of the urine. A diet restricted in BCAAs was started on day 6. The odour of maple syrup disappeared by day 10.

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She progressed well and reached her developmental milestones as expected. During her first year of life she continued to grow along the 9th centile for weight and the 25th centile for height. At 15 weeks she experienced her first episode of decompensation precipitated by a viral respiratory infection. In all she was admitted to hospital on three occasions before her first birthday. On each occasion she made a full recovery.

Childhood

As no previous infant with MSUD had survived, the clinicians treating her had a low threshold for hospital admission during intercurrent illness, contributing to significant periods spent in hospital.

Before the age of 7 years, she was admitted as an inpatient on 23 occasions with a mean inpatient stay of 11.5 days (range 2–42). An increase in the frequency of admissions to hospitals appears to coincide with documented family dysharmony. Most of the inpatient admissions were associated with vomiting, anorexia, ataxia and, on one occasion, convulsions. When she was 7 years old, her father took over full-time care of her and hospital admissions subsequently became much less common.

At 5 years of age, lens opacities were first noticed by the school ophthalmologist. She was found to have bilateral corneal opacities, which were blackish-brown in colour, dense, discrete and 0.5 mm in diameter. They were observed during each subsequent clinic visit and continued to progress slowly.

Adolescence and early adulthood

Menarche was reached at 11 years 9 months, when the patient weighed 33.7 kg. At 19 years of age she became pregnant but, for social reasons and owing to the uncertainty surrounding the possible outcome of pregnancy, a termination was performed at 18 weeks of gestation. There were no fetal abnormalities apparent. She married at 26 years of age, and two years later became pregnant again, but had incomplete spontaneous abortion. On dilatation and curettage, a CIN II lesion of the cervix was found that was subsequently treated with laser therapy. The cataracts continued to progress slowly.

Adulthood

At 30 years of age the patient divorced. Four months later she developed hypotension thought to be due to thioridazine sedative treatment. This coincided with a period of anorexia and weight loss of 4.5 kg. She had another relationship, but her partner died when she was 34 years old. She was treated with a short course of lofepramine 140 mg nocte for clinical depression and made a good recovery.

At 36 years, an intercurrent illness caused anorexia and weight loss. On her admission to hospital it became clear that she was not taking all her protein exchanges. Later that year, she had a right lens implant under local anaesthesia. Her left cataract was kept under observation.

She had a right ankle fracture at 40 years due to a high velocity injury when she slipped and fell. Her bone density z-scores were -0.9 in the hip and -1.2 in the lumbar spine.

Currently she is doing well. Physical examination reveals only a fine resting tremor and normal reflexes. She weighs 61 kg and is 1.59 m tall, thus giving her a body mass index of 24.1 kg/m^2.

Intelligence and mental development

First year

The patient was reviewed by a clinical psychologist at 3, 35 and 55 weeks and neurodevelopment was considered to be normal.

Childhood

At 3 years 2 months, her development quotient (DQ) was estimated to be 97. Her intellectual quotient (IQ) was estimated at 79 (30th centile), but the tests were difficult to perform. At 3 years 9 months she was again reviewed by a clinical psychologist. Her IQ was estimated to be 92 using the revised Stanford Palmer test. This was considered to be in keeping with IQs of the rest of the family.

Initially she attended a school for the disabled, but all her school reports indicated good progress and she was thought to be similar to any healthy 8-year-old. At the age of 9 she was transferred to a state primary school. Her behaviour was normal but she needed special help with reading. Her school reports over the next 4 years varied from average to good and she was found on all subsequent school assessments to be physically and intellectually normal. As a teenager she continued in the local state comprehensive school, although she was in the lowest class stream. At 16 years of age her school report indicated that she was slightly immature and that it would be preferable if she remained at school for another year. This was confirmed when she was assessed as a 17-year-old by a consultant psychiatrist, who described her as an emotionally immature girl. She left formal education at 16 years of age with CSE passes in English, maths, science and community studies.

Adolescence and early adulthood

She obtained full-time employment as a packer in a factory and later worked in a steam laundry. Her early adulthood

was characterized by family social problems and she moved out of the home on several occasions. In her early twenties matters settled down and she has been working as a cashier at a supermarket chain for over 15 years.

Adulthood

She continued to further her studies as an adult and participated in several night classes where she completed most of the courses studied. She continues to study for GCSE maths and English qualifications. She also acts as a carer for her current partner who has Usher syndrome.

At the age of 42 she was assessed neuropsychometrically. Her executive function ranged from borderline to average and her memory was considered to be average. Her verbal comprehension was between the 9th and 24th centiles, memory between the 2nd and 8th centiles. Using the WAIS III index, verbal IQ was 78 and performance IQ 74. The WTAR index placed her verbal IQ at 84.

The dietary regimen

First year

The original investigations of dietary manipulation were performed on the elder sibling (Westall 1963). It was concluded that the high plasma BCAA levels could be normalized by limiting specific amino acids. The original diet used the amino acid content of milk as a basic reference point. Leucine, isoleucine and valine were restricted to a level where growth was not affected, while the rest of the required amino acids were added as supplements.

Childhood

As a toddler, she remained on a strict diet. Her parents were trained in the use of the supplement. At that time, no specific commercial supplements were available and most were prepared in-house. Growth was monitored carefully. As a 3-year-old the patient received 32 g protein per day in combination with three Ketovite tablets and 5 ml of liquid. She also had 20 g of in-house amino acid mixture, two in-house mineral and trace element mixtures, 85 ml of arachis oil and 5 ml of Acacia powder. At that time she had no interest in food and was content to remain on the same regimen despite efforts to improve the taste and increase variety. As a 10-year-old she was given 18 g of protein, 20 g aminoA mix, 25 g MSUD Aid, 8 g mineral mix. This was slowly increased and as a 16-year-old she received 18 g of protein, 50 g MSUDAid, 8 g Aminogran mineral mix, 25 ml Proparol, and Ketovite 3 tablets and 5 ml liquid.

Adolescence and adulthood

As an 18-year-old she received 18 g of protein, 75 g MSUDAid, 8 g Aminogran mineral mix, 50 ml Proparol, and Ketovite 3 tablets and 5 ml liquid. When she was 28 the MSUDAid was reduced to 60 g and one sachet of Phlexyvits replaced the Proparol, while 100 g Duocal was added. At 35 years of age the MSUDAid was increased to 80 g and when she turned 40 she started taking four MSUD Express sachets per day.

Biochemical investigations

Plasma amino acids in cord blood and urine organic acids for the first three days of life were normal. The urinary excretion of keto acids (α -oxoisocaproic, α-oxo-β-methylvaleric and α-oxoisovaleric acid) rose on day 4. On day 6, BCAAs were 10–20 times higher than the reference range (valine 2051 μmol/L, isoleucine 1374 μmol/L, leucine 3969 μmol/L). After commencement of diet, urinary keto acids gradually decreased and were within the reference range by day 13.

BCAA concentrations are summarized in Table 1 and Figure 1. During the first 10 years of life her control was good overall but varied due to intercurrent illness that caused significant rises in all BCAAs. The variation in control improved in her second decade. From her third decade control has remained reasonable, although not ideal, and the results indicate a possible slight relaxation of the diet despite the availability of better and more palatable supplementation products.

Table 1 Branched-chain amino acid levels (μmol/L; mean ± SEM). Normal ranges are indicated for each amino acid

	Valine (μmol/L) (137–462)	Isoleucine (μmol/L) (31–115)	Leucine (μmol/L) (72–297)	Allo-isoleucine (μmol/L)
0–10 years	589.7 ± 111.1	350.9 ± 68.7	846.9 ± 206.0	152.6 ± 15.3
10–20 years	350.4 ± 34.2	183.1 ± 7.6	373.9 ± 53.4	106.8 ± 15.3
20–30 years	457.0 ± 40.1	241.2 ± 12.6	646.3 ± 66.9	109.2 ± 9.1
30–40 years	632.1 ± 19.2	252.1 ± 9.4	791.1 ± 22.5	99.7 ± 4.1
40–43 years	604.6 ± 33.7	272.6 ± 15.5	790.1 ± 36.1	88.9 ± 3.5

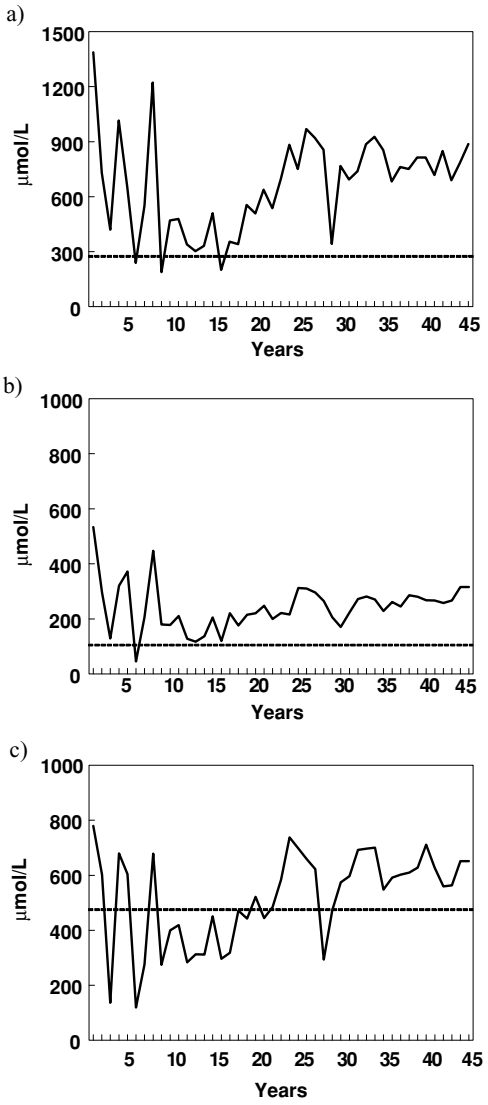

Fig. 1 Mean annual concentrations of (a) leucine, (b) isoleucine and (c) valine. Broken line indicates the upper limit of reference range

Discussion

This report documents the clinical progress of the longest-surviving patient with maple syrup urine disease. The case suggests that patients can continue to live a normal life into their fifth decade without any serious or unexpected complications. The patient has maintained a good standard of living, with good quality of life. She has been able to fulfil her potential and aspirations no differently from others within her family. Her case shows that rises in blood levels of BCAAs are usually associated with illness or periods of psychological stress that contribute to poor compliance. It also shows that BCAA concentrations consistently much higher than the normal ranges do not appear to have a detrimental effect on neuropsychometric outcome.

Her growth as a child was within normal limits as she grew between the 25th and 50th centiles for height and the 9th and 25th centiles for weight. As an adolescent and young adult she had problems with weight gain and both illness and psychological stress readily resulted in anorexia and weight loss. It is interesting to note that at 11.7 years her menarche was associated with a body weight of only 33 kg. Her lowest recorded weight as an adult was 39 kg and the highest 60.9 kg. The largest weight gain was 10 kg in one year, which occurred between 38 and 39 years of age, not associated with any significant alteration in BCAAs.

She has probably reached her genetic potential regarding intellectual development. During her school years she was deemed to develop normally and it was only in her late adolescence that immaturity was noted. After leaving school it was difficult for her to maintain full-time occupation, but during the last two decades she has remained in one position. Her IQ places her below average, but she continues to function normally within society. This level of intellectual development compares favourably with that of younger patients described in other series: twenty French patients, the oldest 16 years, 3 patients of 'normal' intelligence, 12 patients 'mildly retarded to low average' intelligence (Rousson and Guibaud 1984); eight US patients, oldest 16 years, mean verbal IQ 83 $\pm$ 10, mean performance IQ 68 $\pm$ 9 (WISC-R 1974) (Nord et al 1991); and 22 German patients, oldest 16 years, mean IQ 74 $\pm$ 14 (range 50–103, Snijders–Oomen intelligence test) (Hilliges et al 1993).

The patient became pregnant on two occasions. On the first occasion she underwent a termination of pregnancy; and on the second she had a spontaneous abortion. Successful pregnancy has been reported in women with MSUD (van Calcar et al 1992). She developed bilateral cataract from an early age and subsequently underwent surgery with lens implantation. Cataract has not been reported in MSUD before, although other ocular manifestations including optic atrophy, grey optic papilla, nystagmus, ophthalmoplegia, strabismus, de-epithelialization of the cornea and cortical blindness have previously been described (Burke et al 1991; Tornqvist and Tornqvist 1996). She has osteopenia with a single traumatic fracture.

She maintains her diet with some degree of success. Her life-time has charted the many changes in supplements that have become available for these patients and currently she is on a low-volume complete formula that has improved her cobalamin and folate status. It is noteworthy that the prolonged periods of raised plasma levels of BCAAs appear not to have had dramatic influences on her general health and well-being. Target ranges for BCAAs in MSUD patients for long-term therapeutic goals are unclear. Despite her less than ideal compliance with the diet, she continues to do well and has not developed any new or progressive neuropathology. Her progress over the next 40 years will be of great interest

to all clinicians following patients with inherited metabolic disorders into adulthood.

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