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Nota Clínica

3-hydroxy-3-methylglutaryl-CoA lyase deficiency: a case report and literature review *Deficiencia de la 3-hidroxi-3-metilglutaril-CoA liasa: un caso clínico y revisión de la literatura*

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Abstract

Key words:

3-hydroxy-3-methylglutaryl-CoA lyase deficiency. Leucine. Protein. Hypoglycemia. Metabolic acidosis.

Introduction: 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency is an autosomal recessive disorder that usually presents in the neonatal period with vomiting, metabolic acidosis, hypoglycemia and absent ketonuria. Few cases are reported in the literature, and optimal dietary management and long term outcome are not fully understood.

Case report: We report a 2 year old girl with HMG-CoA-lyase deficiency who had limited fasting tolerance on a low protein diet, with several recurrent hospital admissions with severe hypoketotic hypoglycaemia and metabolic acidosis. We also review the dietary management and outcome of other reported cases in the literature.

Discussion: In order to define optimal dietary treatment, it is important to collect higher numbers of case studies with detailed dietary management, fasting times and outcome.

Resumen

Palabras clave:

Deficiencia de la 3-hidroxi-3-metilglutaril-CoA (HMG-CoA) liasa. Leucina. Proteína. Hipoglucemia. Acidosis metabólica.

Introducción: la deficiencia de la 3-hidroxi-3-metilglutaril-CoA (HMG-CoA) liasa es un desorden autosómico recesivo que normalmente se presenta en la infancia con vómitos, acidosis metabólica, hipoglucemia y sin cetonuria. Se han publicado pocos casos en la literatura científica sobre el mejor tratamiento dietético para el adecuado desarrollo de los pacientes a largo plazo, por lo que esta deficiencia no es bien conocida.

Caso clínico: presentamos una niña de 2 años con deficiencia de la 3-hidroxi-3-metilglutaril-CoA (HMG-CoA) liasa. Recibiendo una dieta baja en proteína con una tolerancia de ayuno limitada con episodios recurrentes de admisión hospitalaria con hipoglucemia hipocetótica y acidosis metabólica. También hemos revisado el tratamiento dietético y el desarrollo de otros casos publicados en la literatura científica.

Discusión: es importante recoger más casos clínicos describiendo el tratamiento dietético seguido, el tiempo máximo de ayuno y el desarrollo de los pacientes con el objetivo de definir el mejor tratamiento.

Conflicts of interest: Anita MacDonald has received research funding and honoraria from Nutricia, Vitaflo, Biomarin and Lactalis International. She is a member of the following advisory boards: European Nutritionist Expert Panel (Biomarin), Sapropterin Advisory Board (Biomarin), ELEMENT (Danone-Nutricia), and Arla and Applied Pharma Research. Anne Daly has undertaken evaluation work for the nutritional companies - Vitaflo Ltd, Nutricia Ltd and Metax. Alex Pinto has received an educational grant from Cambrooke Therapeutics and grants from Vitaflo, Merck Serono and Biomarin to attend scientific meetings. Steve Kitchen received sponsorship from Sobi, Nutricia and Vitaflo to attend meetings. All the other authors do not declare any conflict of interest.

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INTRODUCTION

3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency (3-hydroxy-3-methylglutaric aciduria), an autosomal recessive disorder, is caused by several mutations in the HMG-CoA Lyase gene (1,2). It was first described in 1976 (3). It is associated with mitochondrial HMG-CoA lyase enzyme deficiency, which has an important role in the ketogenic pathway and is the last step in leucine catabolism (1,4-6) leading to inadequate ketone body synthesis (7) and accumulation of toxic metabolites (4) of leucine catabolism (Fig. 1). It occurs in 1 in 100,000 live neonates (1), although this may be an underestimate due to sudden infant death and misdiagnosis with Reye's syndrome. It is more common in Saudi Arabia, Portugal, Spain and Pakistan (1) with a high incidence of parental consanguineous marriage reported in documented cases (4,8-11). It is suggested that HMG-CoA-lyase deficiency should be added to newborn screening panels (12), although further studies are necessary to demonstrate its effectiveness.

Although there is considerable heterogeneity, patients usually present in the first year of life (7,8,13,14) with vomiting, hypotonia, metabolic acidosis, hypoketotic hypoglycaemia (7,15), and hepatomegaly, and it is usually triggered by illness or fasting. In acute episodes, hypothermia, lethargy, apnoea, coma and even death may ensue if untreated (7,14-17). Pancreatitis (15,18) and cardiomyopathy (1,14,19) are less common long term complications. There is increased excretion of the following urinary organic acids: 3-hydroxy-3-methylglutaric acid, 3-methyl-glutaric acid, 3-methyl-glutaconic acid and 3-hydroxy-isovaleric acid (6,14,20). Abnormal liver function tests, raised lactate and hyperammonaemia may occur. Most children have normal developmental progress with appropriate treatment (1,5,21), but recurrent metabolic decompensation may result in neurological deficit including stroke-like episodes (22). On treatment, urinary organic acids improve but still remain abnormal (23).

The primary aim of management is rigorous emergency management, with high carbohydrate intake during infection and avoidance of extended fasts (16-18), with dietary protein and possibly fat restriction. In early childhood, metabolic decompensa-

tion is rapid with acidosis a common feature requiring intravenous administration of glucose and sodium bicarbonate if acidosis is severe (4,7). There are few published case studies and optimal dietary management is not clearly established. Carnitine supplementation is prescribed if serum levels are low.

In this paper we present the dietary management of a 2 year old girl with HMG-CoA-lyase deficiency cared for by Royal Stoke Hospital and Birmingham Children's Hospital, UK. The parents gave consent for this case to be published. We also review the dietary management of published case reports of HMG-CoA-lyase deficiency. A comprehensive search was conducted up until December, 2016 using PubMed, ScienceDirect, Scopus and Google Scholar. Search terms were as follows: '3-hydroxy 3-methylglutaric aciduria', '3-hydroxy-3-methylglutaryl-CoA lyase deficiency', 'HMG-aciduria and diet', 'HMG-CoA lyase deficiency and diet'.

CASE REPORT

A female infant of Pakistani origin was born at 37 weeks gestation via normal delivery following a pregnancy complicated by maternal gestational diabetes, significant morning sickness and fatigue. Her birth weight was 2.8 kg and parents were distant cousins. At 4 months of age she had developed colic and intermittent vomiting commonly after feeding.

At 5 months of age, she was admitted to hospital with rapid breathing after a short history of vomiting. On admission she was hypotonic, pale and unresponsive and parents reported her urine has an unusual odour. She had severe non ketotic hypoglycaemia (glucose: < 0.6 mmol/L), very low blood ketones, and metabolic acidosis (pH 7.17; pCO₂: 4.63 kPa; HCO₃: 13.1 mmol/L), requiring intravenous infusion with glucose and *Trometamol* respectively. Her free fatty acids (FFA) were 2821 μ mol/L, 3-hydroxybutyrate < 50 μ mol/L (in normoglycaemia reference range is FFA, 600 μ mol/L and 3-hydroxybutyrate, < 300 μ mol/L), and FFA/3-hydroxybutyrate ratio > 50 (reference range < 2.0). Lactate was moderately elevated (3.1 mmol/L). She was ventilated and subsequently extubated the following day. She was hypothermic (35.4 °C) with a

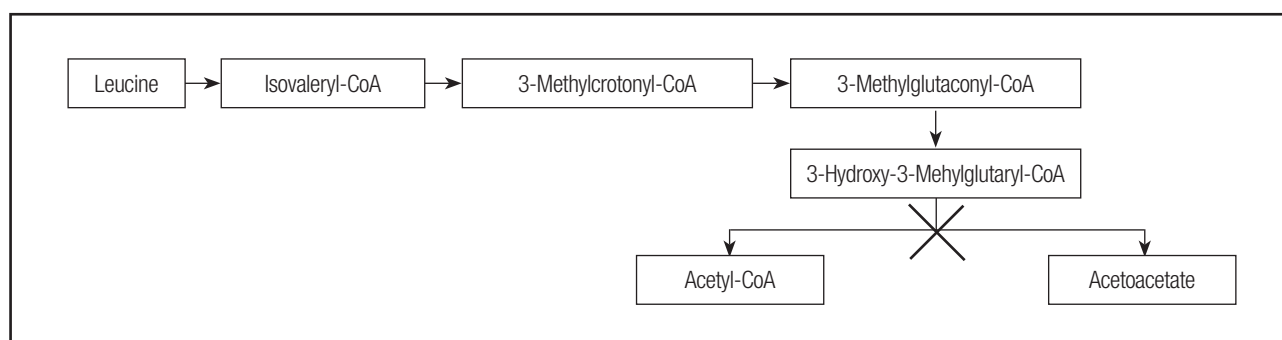


Figure 1.

The leucine catabolic pathway in patients with HMG-CoA lyase deficiency.

stable cardiovascular status. The hyperammonaemia (535 $\mu\text{mol/L}$) normalised with dextrose. She required a blood transfusion for anaemia (Hb, 55 g/L). Initially her INR level was 1.6, associated with a degree of liver dysfunction, and she was given vitamin K. Her weight was < 9th percentile. There were no clinical signs of infection and respiratory distress. Her metabolic investigations were consistent with HMG-CoA-lyase deficiency showing grossly increased urine 3-hydroxyisovalerate, 3-methylglutaconate, 3-hydroxy-3-methylglutarate (HMG) and methylcrotonylglycine. There was a marked dicarboxylic aciduria (particularly glutarate, adipate, octenedioate, suberate, sebacate, 3-hydroxysebacate and 5-hydroxyhexanoate. There was also grossly increased plasma hydroxy-C5 carnitine 1.31 $\mu\text{mol/L}$ (reference range ≤ 0.08). The plasma free carnitine was 13 $\mu\text{mol/L}$ (reference range 13 to 52 $\mu\text{mol/L}$). DNA analysis was not performed.

She commenced continuous 24 hour nasogastric (NG) low protein feeds which consisted of a combination of standard infant formula and protein-free infant formula (*Energivit*[®], Nutricia[®]) providing: protein, 1.5 g/kg/day; energy, 120 kcal/kg/day; and fat, 6.3 g/kg/day. Fat intake remained unrestricted. The percentage of energy provided by protein, fat and carbohydrate was 5%, 47% and 48% respectively. Her emergency feeding plan consisted of 10% glucose polymer with a maximum fasting time of 3 hours. Carnitine (100 mg/kg/day) supplements were prescribed. She was discharged home on a feeding plan of 3 to 4 hourly feeds but her oral feeding was poor and she struggled to achieve prescribed feed volumes. She began 'top up' bolus NG tube feeds at the age of 8 months to ensure a minimal feed target was met. Assessment of her fasting tolerance (Table I) at 10 months indicated a maximum safe fasting time of only 7 hours with free fatty acids elevated to 1327 $\mu\text{mol/L}$ at 7 hours. Her blood ketone levels were < 50 $\mu\text{mol/L}$ throughout the fast, which is consistent with a ketone synthesis defect.

By 11 months of age she had required 11 hospitalizations, presenting mainly with recurrent vomiting, metabolic acidosis and hyperammonaemia without obvious contributing factors, although she had commenced histamine H2 receptor antagonists (*rانيتidine*) and *gaviscon*. In 3 of the admissions, she required intraos-

seous cannulation due to poor venous access in order to correct acidosis and hypoglycaemia. Some of the hypoglycaemic attacks were attributed to poor adherence with the feeding plan as there were a number of family social issues. At 11 months of age, due to the persistent metabolic instability and feeding difficulties, she commenced overnight continuous nasogastric tube feeds with two to three hourly feeds day-time feeds. She remains on 1.5 g/kg/day natural protein without leucine-free L-amino acid supplementation. Her enteral feeds were based on a standard infant formula (to meet natural protein requirements), supplemented with a protein-free infant formula and low protein solids. She had a percutaneous endoscopic gastrostomy (PEG) insertion at 13 months of age.

Since commencement of overnight feeding, she has had two further hospital admissions; one due to PEG insertion and one associated with gastroenteritis. She is 2 years old and her developmental progress is within normal limits. Her weight is between the 25-50th percentile and her length is on the 25th percentile.

DISCUSSION

This is a report of a young child with HMG-CoA lyase deficiency with limited fasting tolerance who developed severe and repeated hypoglycaemia without obvious contributing factors. At the age of 10 months, her metabolic response to a fasting time of 7 hours was associated with increased free fatty acids (suggesting increased fatty acid oxidation) despite normal blood glucose (Table I). This led to the introduction of overnight continuous tube feeding without further reported reoccurrence of unexplained hypoglycaemia following 13 months follow-up. Earlier reports (9,15,20,24,25) have described death and serious morbidity in acute crisis which underlines the need for prompt diagnosis and attentive treatment.

There is limited published evidence about the safe fasting times in HMG-CoA-lyase deficiency. It has been suggested that it may be reasonable to continue a night feed until the age of 1 year, but

Table I. Fasting tolerance test result for case study at the age of 10 months

	Plasma glucose $\mu\text{mol/L}$	Plasma lactate $\mu\text{mol/L}$	Free fatty acids $\mu\text{mol/L}$	3-hydroxybutyrate $\mu\text{mol/L}$
Baseline	5.6	2.2	323	< 50
1 hour	5.6	1.2	450	< 50
2 hours	5.0	2.1	596	< 50
3 hours	4.9	1.6	408	< 50
4 hours	4.9	2.5	675	< 50
5 hours	4.9	2.0	946	< 50
6 hours	4.8	6.0	N/A	N/A
7 hours	5.1	3.2	1,327	< 50
7.5 hours	N/A	N/A	N/A	N/A
8 hours	N/A	N/A	N/A	N/A

for older children overnight fasting (10 to 12 hours) is considered safe (26). However, a boy (24) with HMG-CoA-lyase deficiency who was diagnosed in the neonatal period and had been carefully treated with a low protein and fat restriction, died unexpectedly at 13 months of age in his sleep. His maximum nocturnal fasting time was 8 hours. Necropsy indicated no signs of infection. His death was attributed to fasting hypoketotic hypoglycaemia. François et al. (20) assessed the response to fasting in a 8 month old child with HMG-CoA lyase deficiency. When the first post fasting blood samples were analysed at 11 hours, high free fatty acid concentrations (approximately 1,000 $\mu\text{mol/L}$), with a blood glucose of 3 were observed. The authors suggested overnight feeding may be beneficial.

There is little evidence to support optimal dietary treatment and recommendations have varied for protein, leucine and fat restrictions (4,6,9,15,24,27). Commonly, dietary treatments are combined so the importance of each dietary component is not well established. More case reports have prescribed dietary protein restriction with less emphasis on the ketone body and fatty acid metabolism defect (Table II).

The severity of protein restriction is variable, with some advocating a moderate protein restriction only (6,26,28,29) and others recommending a leucine restriction as low as 50 mg/kg/day (30). Many case studies report a leucine intake of 50 to 150 mg/kg/day, i.e. equivalent to approximately 0.5 to 1.5 g/kg/day of natural protein (6,10,24,25,29,31-33). Leupold et al. (29) showed a 5-fold increase in urinary metabolites when natural protein increased from 1.8g to 2.5 g/kg/day (29). In one case study, a five-fold increase in 3-hydroxy-3 methylglutaric acid was observed following one meat meal (10). Dasouki et al. (1987) reported that urinary organic acids improved on a diet providing only 87 mg/kg/day of leucine and 2 g/kg/day total protein (presumably supplemented with leucine free amino acids but unreported) and 25% of energy as fat. In a child with HMG-CoA-lyase deficiency, a 750 mg (100 mg/kg/day) leucine load led to increase in leucine metabolites (6). Estimated safe leucine requirements for children and adults are 54 mg/kg/d and 40 mg/kg/d, respectively (34).

Leucine has an important role in protein synthesis (34) and any over restriction may potentially result in weight loss (35) and triglyceride lipolysis (36), subsequently leading to amino acid imbalance and metabolic decompensation. This is a potential risk if the glucose based emergency feeds are used excessively. The use of leucine-free L-amino acids is not well reported in HMG-CoA-lyase deficiency. They should only be necessary if WHO safe levels of protein intake are not met by natural protein restriction and only a few reports (10,29,31,37) describe their use. Shilkin et al. (10) reported one patient who refused the prescribed leucine free formula and so followed a self-restricted protein diet only.

Our case study, similar to other case reports (4,31) was not on a restricted fat intake but some fat restriction may have been beneficial. Defects in fatty acid catabolism may play an important role in metabolic decompensation. Some case reports limit fat intake to 20 to 30% of total energy intake (6,10,29). In one report, excretion of leucine metabolites increased significantly (3-hydroxy-3-methylglutaric acid, 3-methyl-glutaconic acid, 3-methyl-glutataric acid and 3-hydroxyisovaleric acid) when fat

intake was increased from 15 g to 40 g/day in 2 children with HMG-CoA-lyase deficiency (6). Walter et al. (25) showed in a 9 month old infant, that progressive fat restriction (3.1 g/kg/day to 1.7 g/kg/day) lowered urinary excretion of 3-hydroxy-3-methylglutaric acid and 3-methyl-glutaconic acid despite a dietary leucine increase from 50 up to 150 mg/kg/d.

Uncooked cornstarch may have a role in the management of HMG-CoA lyase deficiency by helping extend fasting tolerance but there are only 2 case reports that describe its use. Gibson et al. (1990) reported a clinically stable 13 month old male who was given 1.5 g of uncooked cornstarch before sleeping, together with a low protein and modest fat restriction. In another case report (38), a 3 month old child with severe hypoglycaemia was prescribed a leucine restricted diet together with uncooked cornstarch (dose unavailable). She had a fasting tolerance of 18 hours at 12 months of age and dietary treatment stopped when she was 4 years old. The use of uncooked cornstarch warrants further investigation in this condition.

Patients with HMG-CoA lyase deficiency may develop hypoglycaemia and metabolic acidosis very quickly during fasting or intercurrent illness (20), leading to coma and sudden death (4,7,17,24). Thompson et al. (1990) showed in 6-year-old twins with HMG-CoA-lyase deficiency that protein mobilization and leucine oxidation play important roles during infection but not during fasting. During infection, leucine turnover, oxidation and plasma concentrations markedly increase leading to an elevation in urinary organic acids; but during fasting, fatty acid catabolism was considered to lead to a higher production of leucine metabolites. Although glucose polymer emergency feeds should be initiated on the first sign of illness, our case study commonly failed to tolerate these feeds, leading to a potential delay in starting intravenous glucose and bicarbonate to correct metabolic acidosis (7). There may be a role for commencing home NG tube feeding with emergency feeds on the first sign of illness to ensure adequate and continuous supply of glucose and fluid intake.

CONCLUSIONS

Overall there is limited clinical experience with the management of patients with HMG-CoA lyase deficiency and published case studies suggest a wide clinical heterogeneity. The optimal dietary treatment remains undefined and the rigorosity of therapy is likely to be influenced by the severity of each case. This case study exhibited limited nocturnal fasting tolerance and poor metabolic control when treated with a low protein diet only. Establishing disorder severity at an early stage of management is essential to optimise clinical outcome. Evaluating fasting tolerance immediately post diagnosis will help establish the requisite for night feeding in individual cases. With all rare disorders requiring dietary management it is important to monitor clinical progress, document dietary intake and biochemical markers carefully in order to systematically evaluate the role of nutritional intervention. It is necessary to collect higher numbers of case studies with detailed dietary management, fasting times and outcome in order to improve future treatment.

Table II. Characteristics of patients with HMG-CoA-lyase deficiency

Patient	Ref	Gender	Country of origin	Consanguinity	Diagnosis		Diet				Outcome
					Age of diagnosis	Clinical symptoms	Dietary prescription	Leucine/Protein prescription	Amino acid formula	Fasting tolerance	
Current case study		F	UK (Pakistani origin)	Yes	5 months	Coma, metabolic acidosis, non ketotic hypoglycemia, hyperammonaemia, hyper-lactatemia	Nocturnal nasogastric feeds	Low protein (1.5 g/kg/day)	No	≤ 7 hours	Age 2 years: normal growth and development
1	(15)	F	N/A	No	5 years	Acidosis, intractable vomiting, abdominal tenderness, acute pancreatitis	High CHO Low fat	Low leucine	No	-	6 yrs: growth, development, and school performance are normal
2	(24)	M	N/A	N/A	46 hours	Metabolic acidosis, hypoglycemia, hyperammonaemia, hyper- lactatemia and altered hepatic enzymes	Low fat (5 g/kg/day) High CHO (22 g/kg/day) High fluid (180 ml/kg/day)	Low protein (1.5-2 g/kg/day)	No	< 8 hours	13 months: died suddenly in his sleep without any sign
3 ^y	(4,27)	F	United Arab Emirates	Yes	3 days	Slow respirations, hypothermia, abdominal distention, palpable liver, metabolic acidosis. Elevated transaminases, ammonia, lactic acid pyruvic acid and LDH. Prothrombin time increased; fibrinogen decreased	Low fat (25% of total calories)	Low leucine (87 mg/kg/day) Moderate protein (2 g/kg/day)	No	-	15 months: normal growth and development
4	(4, 29)	F	Portugal	N/A	5 months	Head circumference > 90 th percentile, mild metabolic acidosis and mild hypoglycemia	-	Low leucine (80-100 mg/kg/day) Low protein	Leucine free formula	-	3 years: severely delayed development, only walks with support

(Continue in the next page)

Table II (Cont.). Characteristics of patients with HMG-CoA-lyase deficiency

Patient	Ref	Gender	Country of origin	Diagnosis		Diet				Outcome
				Age of diagnosis	Clinical symptoms	Dietary prescription	Leucine/Protein prescription	Amino acid formula	Fasting tolerance	
5	(37)	F	China	4 years	Status epilepticus, hypoglycemia, and severe metabolic acidosis	2100-2200 kcal/d Lipid (24%) CHO (63%)	Leucine (1,000 mg/day) Protein (1.5-2 g/kg/day)	Leucine free formula with maltodextrin	Avoidance of starvation	13 years: no episodes of metabolic decompensation or hypoglycemia during follow-up
6 ^y	(9)	F	Saudi Arabia	4 days	Severe lactic acidosis, hypoglycaemia and coma	Low fat (30%)	Low leucine (87 mg/kg/day)	No	-	3 yrs: normal developmental assessment, mild changes in MRI of brain
7 ^y	(9)	F	Saudi Arabia	40 days	Lethargy, mild spastic quadriplegia with exaggerated reflexes	Low fat (20%)	Low leucine (80 mg/kg/day)		-	3 years: normal developmental assessment
8 ^y	(9)	F	Saudi Arabia	24 hours	Devastating metabolic acidosis, hypoglycemia, lactate 20 mmol/l	Low fat (30%)	Low leucine (87 mg/kg/day)	Low Leucine Formula	-	9 months: developmental delay
9 ^{y*}	(9)	M	Saudi Arabia	2 months	Due to previously sibling death	Low fat (30%)	Low leucine (80 mg/kg/day)	No	-	21 months: normal developmental assessment
10	(4,10)	M	Australia	7 months	Diarrhea, vomiting, drowsiness, apnoea attacks, cyanosis, hypoglycemia, metabolic acidosis	High CHO	Low protein	Leucine free formula	-	4.6 years: well and developing satisfactorily
11 [*]	(4,39)	M	Morocco	Prenatal	--	Breast milk + oral glucose	Leucine (50 mg/kg)	No	-	2.5 years: growing and psychomotor development normal
12	(4,11,25)	F	Pakistan	9 months	Respiratory infection, vomiting, metabolic acidosis	Fat (1.7 g/kg/day)	Leucine (150 mg/kg/day) Protein (1.2 g/kg)	No	-	6 yrs: died from illness and diarrhoea

(Continue in the next page)

Table II (Cont.). Characteristics of patients with HMG-CoA-lyase deficiency

Patient	Ref	Gender	Country of origin	Diagnosis		Diet				Outcome
				Age of diagnosis	Clinical symptoms	Dietary prescription	Leucine/Protein prescription	Amino acid formula	Fasting tolerance	
13	(38)	F	Chile	3 months	Seizures, severe hypoglycaemia, metabolic acidosis, hepatomegaly and encephalopathy	CHO (74%) Fat (17%)	Protein (1 g/kg)	No	-	13 years: well nourished, static mild intellectual impairment, deafness and retinitis pigmentosa
14 ⁺⁺	(4,6)	M	USA	8 months	Vomiting, lethargy, tachypnea	Low fat	Low protein	No	-	> 2 years: Developing normally
15 ⁺⁺	(4,6)	F	USA	11 months	Vomiting, lethargy, tachypnea	Low fat	Low protein	No	-	> 2 years: Developing normally
16 ⁺	(4,31)	M	Pakistan	4 months	Poor head control, a divergent squint and roving eye movement	-	Natural protein (1 g/kg)	Leucine free formula	-	1.6 years: Developing normally, good health
17 ⁺	(4,31)	F	Pakistan	4 months	Diagnosed after diagnosis	-	Natural protein (1 g/kg)	Leucine free formula	-	1.6 years: Developing normally, good health
18	(4,33)	F	Chile	3 months	Vomiting, rapid onset of coma, profound hypoglycaemia, hepatomegaly	-	Leucine (120 mg/kg) Protein (2 g/kg)	No	-	1.5 years: Progressing well
19	(4,32)	M	USA	14 months	Lethargy, cold, vomiting, hypoglycemia	-	Low leucine	MSUD formula	-	2 years: Normal physical development, slightly delayed mental development

*Twins. *Siblings. ++Double first cousins. *Carnitine supplementation (100 mg/kg/day).

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