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DIALYSIS / ORIGINAL ARTICLE

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Utility of hemodialysis in maple syrup urine disease

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Abstract Maple syrup urine disease (MSUD) is an inborn error of metabolism stemming from a deficiency in 2-ketoacid dehydrogenase and resulting in the systemic accumulation of branched chain amino acids (BCAAs). Affected children may suffer profound developmental and cognitive impairment from exposure to high levels of BCAA and their associated neurotoxic metabolites. Endogenous renal clearance of BCAA is limited and several therapeutic modalities including intensive nutritional regimens, exchange transfusions, peritoneal dialysis, and continuous hemofiltration have been utilized in neonates with MSUD, all of which have had varying success in reducing systemic BCAA levels. In this report, a symptomatic 7-day-old 3-kg neonate with MSUD underwent treatment with a combination of early hemodialysis and aggressive enteral feedings of a metabolically appropriate formula. This approach results in a 75% reduction of systemic toxin levels within 3 h. When compared to other reported modalities of therapy for symptomatic neonates with MSUD, this approach appears to be most efficacious. Moreover, by minimizing the amount of time that an affected neonate is exposed to neurotoxic levels of BCAAs, long-term developmental and cognitive capabilities may be preserved.

Keywords Maple syrup urine disease · Branched chain amino acids · Ketoacid · Hemodialysis · Neonate

Introduction

Maple syrup urine disease (MSUD), an inborn error of amino acid metabolism due to deficient 2-ketoacid dehydrogenase, results in the significant accumulation of the branched chain amino acids (BCAAs) leucine, isoleucine, and valine and their associated neurotoxic metabolites. Cerebral edema and its potentially acute lethal sequelae as well as profound long-term psychomotor developmental delay are well-recognized complications of MSUD [1]. Because of avid proximal tubular reabsorption of filtered BCAAs, endogenous renal clearance of BCAAs is limited and treatment of symptomatic neonates with MSUD focuses on reducing plasma BCAA levels either by anabolic incorporation into newly synthesized protein or by removal from the intravascular space [2]. Several therapeutic modalities including intensive nutritional regimens, exchange transfusions, peritoneal dialysis, and continuous hemofiltration have been utilized in neonates with MSUD, all of which have had varying success in reducing systemic BCAA levels. In this report, we describe a 7-day-old infant with MSUD who was successfully treated with a combination of hemodialysis and aggressive enteral feeding, resulting in very rapid biochemical and symptomatic recovery. We also compare the rate of clearance of BCAAs using this modality with rates of clearance reported in the literature for other therapeutic modalities. We believe that this case and literature reviews demonstrate that prompt hemodialysis combined with enteral feeds of a metabolically appropriate formula is an optimal approach in the management of infants with symptomatic or severe MSUD.

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Case report

A 7-day-old girl presented for evaluation of poor feeding, lethargy, and irritability. There was no history of fever, vomiting, or diarrhea and since birth the child had been taking a commercially prepared iron-fortified formula. The baby was the 2.98-kg product of a 39-week gestation to non-consanguineous healthy parents. After an uneventful nursery course, the baby had been discharged at 2 days of age. At home, the child initially thrived but now was difficult to arouse and the parents noted a peculiar odor to her urine.

The admission physical examination showed an afebrile, normotensive 3-kg infant with mild tachycardia (pulse 150/min) and tachypnea (respiratory rate 36/min). Significant findings included fluctuating lethargy and irritability, hypertonic posturing, and depressed deep tendon reflexes. Pertinent laboratory data included

Table 1 Leucine levels during the course of therapy

Time (h)	Leucine level[a] (μmol/l)	Comment
0	3260	Initiation of hydration and BCAA-free formula
3	3217	Initiation of hemodialysis
7	814	Cessation of hemodialysis
8	1004	Continued enteral feeds with BCAA-free formula
21	997	
33	638	
47	98	
59	14	Leucine added to BCAA-free formula
75	51	Transition to combination of BCAA-free formula and regular infant formula
86	79	
104	85	

[a] Normal leucine levels 32–153 μmol/l

serum sodium 133 mEq/l, potassium 4.75 mEq/l, chloride 102 mEq/l, bicarbonate 18 mEq/l, BUN 5 mg/dl, Cr 0.3 mg/dl, glucose 85 mg/dl, ammonia 71 μmol/l (normal <65 μmol/l) and lactate 1.0 mmol/l (normal <2.2 mmol/l). Venous blood gas demonstrated pH 7.4, pCO_2 31, and bicarbonate 19 mmol/l. The catheterized urine sample showed 2+ blood and 2+ ketones on the dipstick and microscopy revealed 8–10 rbc/hpf with no casts but abundant needle shaped crystals. Cerebrospinal fluid was clear with 6 wbc/ml, 1 rbc/ml, glucose 44 mg/dl, and protein 105 mg/dl.

The infant's neonatal screen revealed significant elevations in BCAAs by ion exchange chromatography: leucine 3472 μmol/l (normal 32–153 μmol/l), isoleucine 473 μmol/l (normal 35–105 μmol/l), valine 819 μmol/l (normal 68–300 μmol/l), and allo-isoleucine 260 μmol/l (normally undetectable). In addition, urine tested positive for 2,4-dinitrophenylhydrazine.

A diagnosis of MSUD was made. Given the profound elevation in BCAA levels and the child's abnormal neurologic examination, an 8-French double-lumen hemodialysis catheter was placed in a femoral vein. After all extracorporeal dialysis lines were primed with packed red blood cells diluted to a hematocrit of 40% with 5% albumin, hemodialysis was performed for 165 min with a 0.7-m^2 polysulfone hollow fiber dialyzer, a blood flow of 30 ml/min, and a dialysate flow of 500 ml/min. Leucine levels fell from 3217 μmol/l predialysis to 814 μmol/l when dialysis concluded (Table 1).

Concomitant with preparations to start hemodialysis, the infant was given intravenous thiamine supplementation (10 mg/kg/day), and an enteral formula free of BCAAs (ketonex-1) was initiated at a rate to provide 110–130 kcal/kg/day. Supplemental isoleucine (80 mg/kg/day) and valine (80 mg/kg/day) were also given to prevent transitory deficiencies of these essential amino acids and the cessation of protein synthesis and, thus, endogenous clearance of BCAAs by anabolism. Isoleucine and valine levels were closely monitored to ascertain if appropriate supplementation was provided at the above doses.

With the fall in serum leucine levels, the baby became increasingly active and alert while still on the extracorporeal dialysis circuit. After dialysis ended, enteral feeds were continued with the specialized formula and leucine levels continued to fall, reaching 396 μmol/l and then 14 μmol/l over the next 2 days. At this time, leucine actually had to be added to the enteral feeds to prevent arrest of protein synthesis. Over the next few days, the infant was moved onto a combination of BCAA-free formula and regular infant formula and the leucine levels remained normal. An EEG done on the 4th hospital day was normal and the infant was discharged home 11 days after admission with a normal physical and neurologic examination and, after 1 year of follow-up, continues to do well.

Discussion

MSUD is inherited in an autosomal recessive mode with an incidence ranging from 1 in 120,000 to 1 in 290,000 in general newborn screening of American infants [3]. The incidence is much higher in homogeneous populations and has been reported to be as common as 1 in 200 births in certain Mennonite communities in the United States [4]. The affected homozygote infant is unable to degrade effectively the BCAAs leucine, valine, and isoleucine and, as a result, these amino acids and their ketoacid metabolites accumulate in the patient's blood, urine, and cerebrospinal fluid. In neonates, it appears that the accumulation of metabolites due to catabolism is more important than accumulation due to nutritional intake of BCAAs.

The enzymatic defect in MSUD is a deficiency in the thiamine-dependent mitochondrial multienzyme complex branched chain 2-oxo acid dehydrogenase (BCODH). BCODH converts the oxoacids created by reversible transamination of BCAAs into acyl CoA for entry into the Krebs cycle. Leucine and its metabolites appear to be significantly more neurotoxic than valine or isoleucine. Several allelic variants of MSUD have been described and at least five types of MSUD have been discerned by Northern blot analysis of cultured fibroblasts and lymphocytes of patients with MSUD [5].

Although MSUD may present in older babies and children, the most dramatic presentations and devastating sequelae generally arise with neonatal MSUD. The interval between birth and onset of clinical symptoms may range from hours to weeks and appears to be more a reflection of the extent of the actual underlying enzymatic defect than the total protein content of the child's diet [1]. As with this case, the first clinical symptoms are usually lethargy and feeding problems and the urine often emits an intensive, maple syrup-like odor. The BCAA ketoacid metabolites may contribute to a mild anion gap metabolic acidosis and the urinary 2-oxoacids may be detected with the 2,4-dinitrophenylhydrazine test. Hyperammonemia and high lactic acid levels are uncommon.

Long-standing elevations of BCAAs appear to exacerbate the neurologic sequelae and contribute to cerebral edema and persistent increased intracranial pressure [2]. There have been some reports that chronic demyelination as assessed by computed tomography or magnetic resonance imaging appears to correlate with plasma leucine levels [6, 7]. Similarly, there is concern that the risk for long-term neurologic, developmental, and intellectual

Table 2 Comparison of reported therapeutic modalities for neonates symptomatic with MSUD (*N* number of individual patients studied, *CVVH* continuous venovenous hemofiltration, *CAVH* continuous arteriovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *CVVHDF* continuous venovenous hemodialfiltration)

Modality of clearance	*N*	Initial leucine level (μmol/l)	Hours of therapy	% clearance achieved	% clearance per hour
Enteral feeds only [9]	5	3000–3400	120–216	70	0.3–0.6
Modified parenteral nutrition (PN) only [10]	1	2250	11.5	21	1.8
Enteral feeds ± PN [11]	9	1489–3359	60–96	73–88	0.8–1.5
Diet + exchange transfusion (ET) [12]	1	2460	48	65	1.4
Diet + ET [19]	2	2460–3700	15–20	60–72	3.6–4.0
Diet + ET [2]	1	2400–3700	15–20	46–79	2.3–5.2
Peritoneal dialysis (PD) [13]	1	2160	16	27	1.7
PD+IV glucose [14]	1	4615	78	91	1.2
CVVH [15]	1	2186	12.5	48	3.8
CVVH+IV amino acid preparation [17]	1	2600	8	69	8.6
CAVH [16]	1	3290	49	60	1.2
CVVHD [15]	1	2536	12	80	6.7
CVVHDF [15]	1	3818	11	60	5.4
Hemodialysis (HD)+IV glucose [18]	1	2630	3	48	16
HD ± enteral feeds (this report)	1	3217	2.75	75	27

anomalies is inversely related to peak plasma leucine levels at diagnosis or to the amount of time after birth that levels remain in a neurotoxic range [8].

Therapy in the neonate with MSUD focuses not only on removing the toxic metabolites and decreasing rapidly the systemic load of BCAAs but also on establishing adequate nutritional support to establish a protein anabolic state. Unfortunately, even with forced diuresis, native renal clearance of BCAAs is quite low due to efficient tubular reabsorption of filtered amino acids [2]. Various therapeutic modalities have been employed to augment native renal clearance and, thus, reduce serum BCAA levels. Although many of these modalities are effective in achieving some sort of clearance, the rapidity and degree of clearance vary widely (Table 2).

With all therapies, it is vital to initiate proper nutritional support as soon as possible to prevent further catabolism of BCAAs and to incorporate existing excess stores of BCAA into new protein. In fact, there are reports of infants with MSUD who have been treated at presentation with specialized enteral feeds or parenteral nutrition alone [9, 10]. Although this may be an option in infants who are not symptomatic or have low levels of leucine and other BCAAs at diagnosis, it is perhaps not the most efficacious way to lower potentially neurotoxic serum levels rapidly and may place severely ill neonates with MSUD at long-term risk because of a more protracted period of elevated BCAA levels.

Exchange transfusion has also been utilized to decrease BCAA levels [19]. Although this technique can transiently decrease high BCAA levels, without repeated or protracted plasma exchanges, BCAA levels will rise again postexchange as tissue stores of BCAAs reequilibrate.

Peritoneal dialysis has successfully decreased BCAA levels in neonates with MSUD [13, 14, 20, 21]. Clearance with peritoneal dialysis is dependent, however, on several factors including the volume of the peritoneal dialysate dwell, the frequency of dwell exchanges, and inherent properties of the peritoneum that may differ from patient to patient. In a severely ill infant with MSUD, it may be difficult to employ the large dialysate volumes and frequent exchanges that may most rapidly clear high BCAAs to levels that prove less neurotoxic. Even in infants with MSUD who are relatively stable, in the face of severe elevation of BCAA levels, it is likely to take many hours to days to decrease BCAA levels to a range considered safe with peritoneal dialysis alone.

Continuous hemofiltration and hemodiafiltration can also clear BCAAs and their metabolites [15, 17, 22]. Unlike conventional intermittent hemodialysis in which clearance may be achieved rapidly by diffusion down concentration gradients, in continuous dialysis modalities, clearance is most often dependent on convection or solute drag through ultrafiltration. Such clearance is slower than the clearance achieved with conventional dialysis but is ultimately effective because the treatment is continuous rather than intermittent. Since ill neonates often do not tolerate aggressive ultrafiltration, the speed with which BCAA levels may be reduced to normal may be compromised in hemofiltration. Even with the addition of replacement fluid or low volume countercurrent dialysis to continuous ultrafiltration, clearance is still most dependent on convective forces and will proceed in a slower manner [15]. Moreover, the neonate must be kept anticoagulated throughout the course of filtration.

In comparison to all of these other modalities, hemodialysis offers the ability to very rapidly decrease even profoundly elevated BCAA levels. In hemodialysis, clearance depends primarily on the molecular mass of the substance to be cleared and any diffusional gradient between the patient's blood and the dialysate. As substances with low molecular masses, BCAAs are readily dialyzable and, in fact, their clearance approximates the clearance of urea [23]. Thus, as exemplified by the experience with the baby in this report, in a matter of a few hours even profoundly elevated BCAA levels may be rapidly reduced to safer levels by hemodialysis, limiting the total hours of toxic systemic levels of BCAAs, and also allowing for correction of any underlying acid-base or electrolyte anomaly which may accompany the infant's acute

presentation. Advances in hemodialysis technology including smaller caliber vascular access dialysis catheters allow for the consideration of short-term hemodialysis even in premature neonates [24]. Moreover, the rapid decline in BCAA levels on hemodialysis necessitates relatively brief periods of time that the infant needs to be anticoagulated and on an extracorporeal circuit.

As soon as MSUD is diagnosed, and while preparations are ongoing to initiate hemodialysis, enteral feeds of a formula free of BCAAs which supplies at least the age-specific recommended daily allowance of calories and amino acids, supplemented with small amounts of the essential BCAAs isoleucine and valine to prevent a deficiency and promote an anabolic state, must be started. This dietary approach actually augments the clearance of BCAAs as they are incorporated into newly synthesized proteins.

We believe that this combination of rapid hemodialysis and early provision of appropriate enteral feeds offers a therapeutic approach to the infant with symptomatic MSUD or severe elevations of BCAAs with advantages over other more traditional therapeutic modalities. There is evidence from a controlled study of children with MSUD that intellectual and neurologic outcomes appear to be influenced by the length of time after birth that these children are exposed to excessively elevated levels of branched-chain amino and ketoacids [8]. Hemodialysis rapidly clears these moieties and limits the length of time that the neonate is exposed to neurotoxic levels of BCAAs. Thus, infants with MSUD who have neurotoxic levels of BCAAs cleared rapidly by hemodialysis may stand a better chance of exhibiting less developmental or cognitive delay than babies who are not treated or treated by therapies that take significantly longer to lower BCAA levels. Unfortunately, despite its superiority in removing BCAAs, hemodialysis is not as available in infants as in older children or adults. In those facilities with access to personnel trained and experienced in infant hemodialysis, however, the rapid initiation of hemodialysis and early enteral feeds should be considered preferential to other modalities in infants with symptomatic or severe MSUD.

References

1. Ogier de Baulny H, Wendel U, Saudubray JM (1995) Branched-chain organic acidurias. In: Fernandes J, Saudubray JM, Van den Berghe G (eds) Inborn metabolic diseases, diagnosis and treatment, 2nd edn. Springer-Verlag, New York, pp 207–220
2. Saudubray JM, Ogier H, Charpentier C, Depondt E, Coude FX, Munnich A, Mitchell G, Rey F, Rey J, Frezal J (1984) Hudson memorial lecture: neonatal management of organic acidurias – clinical update. J Inher Metab Dis 7 Suppl 1:2–17
3. Levy HL (1973) Genetic screening. Adv Hum Genet 4:389–394
4. DiGeorge AM, Rezvani I, Garibaldi LR, Schwartz M (1982) Prospective study of maple-syrup-urine disease for the first four days of life. N Engl J Med 307:1492–1495
5. Fisher CW, Chuang JL, Griffin TA, Lau KS, Cox RP, Chuang DT (1989) Molecular phenotypes in cultured maple syrup urine disease cells: complete E(1)-alpha cDNA sequence and mRNA and subunit content of the human branched chain alpha-keto acid dehyrogenase complex. J Biol Chem 264:3448–3453
6. Brismar J, Aqeel A, Brismar G, Coates R, Gascon G, Ozand P (1990) Maple syrup urine disease: findings on CT and MR scans of the brain in 10 infants. Am J Neuroradiol 11:1219–1228
7. Muller K, Kahn T, Wendel U (1993) Is demyelination a feature of maple syrup urine disease? Pediatr Neurol 9:375–382
8. Kaplan P, Mazur A, Field M, Berlin JA, Berry GT, Heidenreich R, Yudkoff M, Segal S (1991) Intellectual outcome in children with maple syrup urine disease. J Pediatr 119:46–50
9. Parini R, Sereni LP, Bagozzi DC, Corbetta C, Rabier D, Narcy C, Hubert P, Saudubray JM (1993) Nasogastric drip feeding as the only treatment of neonatal maple syrup urine disease. Pediatrics 92:280–283
10. Berry GT, Heidenreich R, Kaplan P, Levine F, Mazur A, Palmieri MJ, Yudkoff M, Segal S (1991) Branched-chain amino acids-free parenteral nutrition in the treatment of acute metabolic decompensation in patients with maple syrup urine disease. N Engl J Med 324:175–179
11. Morton H, Robinson D, Strauss K, Levy H, Kelley R (1999) Diagnosis, treatment, and outcome of 31 neonates with maple syrup disease. From the Clinic for Special Children, Strasburg, Pennsylvania (personal communication)
12. Hammersen G, Wille L, Schmidt H, Lutz P, Bickel H (1978) Maple syrup urine disease: treatment of the acutely ill newborn. Eur J Pediatr 129:157–165
13. Gortner L, Leupold D, Pohlandt F, Bartmann P (1989) Peritoneal dialysis in the treatment of metabolic crises caused by inherited disorders of organic and amino acid metabolism. Acta Paediatr Scand 78:706–711
14. Sallan SE, Cottom D (1969) Peritoneal dialysis in maple syrup urine disease. Lancet: 2 (7635):1423–1424
15. Jouvet P, Poggi F, Rabier D, Michel JL, Hubert P, Sposito M, Saudubray JM, Man NK (1997) Continuous venovenous hemodiafiltration in the acute phase of maple syrup urine disease. J Inher Metab Dis 20:463–472
16. Ring E, Zobel G, Stockler S (1990) Clearance of toxic metabolites during therapy for inborn errors of metabolism. J Peds 117:349–350
17. Thompson GN, Butt WW, Shann FA, Kirby DM, Henning RD, Howells DW, Osborne A (1991) Continuous venovenous hemofiltration in the management of acute decompensation in inborn errors of metabolism. J Peds 118:879–884
18. Rutledge SL, Havens PL, Haymond MW, McLean RH, Kan JS, Brusilow SW (1990) Neonatal hemodialysis: effective therapy for the encephalopathy of inborn errors of metabolism. J Peds 116:125–128
19. Wendel U, Langenbeck U, Lombeck I, Bremer HJ (1982) Exchange tranfusion in acute episodes of maple syrup urine disease – studies on branched-chain amino and keto acids. Eur J Pediatr 138:293–296
20. Mcmahon Y, MacDonnell RC Jr (1990) Clearance of branched chain aminoacids by peritoneal dialysis in maple syrup urine disease. Adv Perit Dial 6:31–34
21. Wendel U, Becker K, Przyrembel H, Bulla M, Manegold C, Mench-Hoinowski A, Langenbeck U (1980) Peritoneal dialysis in maple syrup urine disease: studies on branched-chain amino and keto acids. Eur J Pediatr 134:57–63
22. Falk MC, Knight JF, Roy LP, Wilcken B, Schell DN, O'Connell AJ, Gillis J (1994) Continuous venovenous haemofiltration in the acute treatment of inborn errors of metabolism. Pediatr Nephrol 8:330–333
23. Gouyon JB, Desgrea J, Mousson C (1994) Removal of branched-chain amino acids by peritoneal dialysis, continuous arteriovenous hemofiltration, and continuous arteriovenous hemodialysis in rabbits: implications for maple syrup urine disease treatment. Pediatr Res 35:357–361
24. Sadowski RH, Harmon WE, Jabs K (1994) Acute hemodialysis of infants weighing less than five kilograms. Kidney Int 45:903–906