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Liver transplantation in maple syrup urine disease

Abstract Maple syrup urine disease (MSUD) is an autosomal recessive disorder. Impaired activity of the branched-chain 2-oxoacid dehydrogenase complex (BCOA-DH) causes accumulation of branched-chain L-amino (BCAA) and 2-oxoacids (BCOA) which may exert neurotoxic effects. Treatment comprises dietary management with strictly reduced quantities of protein and BCAA as well as aggressive intervention during acute neonatal and subsequent metabolic complications. MSUD is regarded as a metabolic disorder with potentially favourable outcome when the patients are kept on a carefully supervised long-term therapy. Up to now, three MSUD patients, exhibiting the classical form of the disease, have received orthotopic whole liver transplantation (OLT). Liver replacement resulted in a clear increase in whole body BCOA-DH activity to at least the level of very mild MSUD variants. These patients no longer require protein restricted diets and the risk of metabolic decompensation during catabolic events is apparently abolished.

Conclusion Considering the overall expenses, risks, and outcome, however, the benefit of OLT, even in the most severe form of MSUD, may not be significantly different from that of a classical strict dietary management. Thus, OLT appears not to represent a specific option in the treatment in MSUD.

Key words Branched-chain amino acids · Maple syrup urine disease · Liver transplantation · Stable isotopes · Metabolism

Abbreviations *BCAA* branched-chain L-amino acids · *BCAA-AT* branched-chain L-amino acid aminotransferase · *BCOA* branched-chain 2-oxoacids · *BCOA-DH* branched-chain 2-oxoacid dehydrogenase complex · *KIC* 4-methyl-2-oxopentanoate · *MSUD* maple syrup urine disease · *OLT* orthotopic liver transplantation

Introduction

Maple syrup urine disease (MSUD; MIM 248600) is caused by an inherited deficiency in branched-chain 2-oxoacid dehydrogenase complex activity (BCOA-DH; EC 1.2.4.4.). Impaired catabolism of the branched-chain 2-oxoacids (BCOA) leads to a marked accumulation of BCOA and the corresponding branched-chain L-amino acids (BCAA) L-leucine, L-valine, L-isoleucine, and L-alloisoleucine, in blood and tissues. The disease is characterised by acute and chronic brain dysfunction induced by high levels of neurotoxic metabolites, primarily 4-methyl-2-oxopentanoate (KIC) and its related amino acid, L-leucine.

MSUD presents as a heterogeneous molecular and clinical phenotype [3]. The severest (classical) form is

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associated with very low amounts (< 2%) of residual BCOA-DH activity in all tissues. In classical MSUD, severe neurological symptoms appear very early after birth. Usually, diagnosis is made during the 1st week of life when the infant suffers from metabolic encephalopathy accompanied by cerebral oedema [2, 3].

Current therapy of MSUD

In MSUD, therapeutic efforts aim primarily at the restoration and preservation of normal functions of the central nervous system. The extremely high blood and tissue concentrations of BCOA and BCAA in the severely ill newborn require emergency treatment, frequently with extracorporeal measures [10], in order to rapidly reduce blood concentrations and to avoid permanent brain damage. With proper clinical management, cerebral symptoms resolve within a few days. The further treatment of MSUD comprises 1) life-long dietary restriction of BCAA in order to maintain blood metabolite concentrations close to normal and 2) aggressive intervention during intercurrent illnesses in order to rapidly reverse the metabolic derangement caused by increased BCOA and BCAA levels [36]. When these strategies are followed carefully, normal somatic growth and normal psychomotor development in MSUD patients can be achieved. The fact that many patients with classical MSUD have a poor intellectual outcome may be attributed to persistent brain damage caused by a delay in diagnosis and/or a delayed start of treatment beyond the first 10 days of life [9, 11, 29]. Although the effects of poor long-term metabolic control and metabolic decompensations on the intellectual development are difficult to evaluate [3, 32], the prognosis for MSUD patients on a strict therapeutic regimen is generally favourable.

Role of the liver in oxidative BCAA disposal

BCAA originating endogenously from protein breakdown or extraneously from the diet are mainly (re)used for protein synthesis. Depending on supply and anabolic demands, a variable portion is diverted into catabolic pathways. Renal clearance is negligible [25]. For degradation, BCAA are converted to the corresponding BCOA by the reversible BCAA-aminotransferase (BCAA-AT) reaction. Further oxidative catabolism proceeds, as indicated above, via the irreversible BCOA-DH reaction. Representing the physiological committed step in overall BCAA disposal, this mitochondrial reaction is highly regulated, primarily by an associated kinase-phosphatase system and by feedback inhibition exerted by reaction products [7, 8]. Oxidative BCAA disposal appears to be a general ability of mammalian cells. In all tissues investigated so far, BCAA-AT and BCOA-DH activities are expressed although at considerably variant levels and enzyme activity ratios [7, 20]. With respect to the physiological role of individual organs in overall mammalian BCAA catabolism, most of the available information originates from rat studies.

In the rat, BCAA-AT activity is high in heart (about 4 U/g wet weight) and kidney, medium in brain and skeletal muscle, but comparably low in liver (ratio about 40:30:10:10:0.5, related to wet weight) (cf. [26]). In contrast, total BCOA-DH capacity is most abundant in liver (about 1.3 U/g wet weight), medium in kidney and heart (about 0.3 U/g wet weight), and low in brain and skeletal muscle (about 0.04 U/g wet weight) [14, 28, 35, 38]. Furthermore, the amount of the dephosphorylated, active form of the enzyme complex differs considerably between tissues, e.g. under normal feeding conditions, the in situ activity ranges from > 90% of total in liver and about 50% in brain and kidney, to < 5% in skeletal muscle tissue [14, 35]. In accordance with the enzymatic data, it was consistently found that BCOA are released from extrahepatic rat tissue preparations when incubated or perfused with BCAA-containing media [cf. 7]. Thus, in the rat, the liver is thought to be the principal organ of oxidative BCAA disposal with the BCOA being supplied mainly from extrahepatic sites, especially muscle tissue (a concept that may be found in standard textbooks) [7].

Appropriate studies in man are far less abundant; however, the available evidence indicates that the interorgan relationships may be quite different in human subjects. Early studies suggested that BCAA-AT as well as BCOA-DH activities are generally lower than in rat tissues and exhibit much less significant differences in organ distribution [6, 13]. Recent biopsy measurements have shown that total BCOA-DH activity in skeletal muscle amounts to about 0.03 U/g wet weight (with < 5% being active at rest) [22, 33, 34] compared to ca 0.1 U/g wet weight in liver (estimated from data in [4, 13]). In vivo studies have indicated that BCOA are rather taken up than released by human skeletal muscle. Consequently, when human muscle is challenged with BCAA in situ, a substantial substrate uptake is observed with a but negligible output of the corresponding BCOA into the circulation [1, 15, 31]. Whole body leucine oxidation is not significantly impaired in patients with liver cirrhosis [16, 18] or end stage liver disease [27]. In a recent stable isotope study, the significance of skeletal muscle (leg), kidney and splanchic bed for overall in vivo leucine metabolism in postprandial subjects was thoroughly investigated. Arterio-venous difference measurements showed that skeletal muscle tissue accounted for about 50% of whole body transamination and oxidative disposal of leucine. About 25% of leucine oxidation was referred to kidney metabolism with most of the substrate supplied as 2-oxoacid from the splanchic bed. Less than 20% of overall leucine oxidation took place in gut and liver and the remainder in other extrahepatic tissues [30].

Taken together, the data on human BCAA metabolism accumulated so far indicate that, unlike in the rat,

skeletal muscle and kidney may be the main sites of oxidative BCAA disposal in healthy humans.

Liver transplantation in MSUD patients

So far orthotopic liver transplantation (OLT) has been performed in three children with classical MSUD treated by diet from the 1st week of life. A 7.5-year-old French gipsy girl (case 1, OLT in 1991) [19, 21] and an 8-year-old Mennonite girl (case 2, OLT in 1997) [12] received OLT because of terminal liver failure caused by hepatitis A virus infection and vitamin A intoxication, respectively. A 2-year-old Spanish boy received OLT (case 3, OLT in 1993) at his parents' request because of delayed psychomotor development, neurological signs associated with MRI abnormalities of the brain, and frequent metabolic decompensations [17]. Biochemical post OLT findings in the Mennonite girl and the Spanish boy have been reported in abstract form only [12, 17], data for the French girl have been communicated in greater detail [19].

In the patients, the high BCAA plasma levels decreased dramatically immediately after start of donor liver perfusion. Near normal levels were reached within about 10 h despite the intense postoperative catabolic stress. In the long-term, in each patient liver replacement resulted in tolerance of a normal protein diet with ca. 2-fold above normal increased plasma levels of BCAA and BCOA (Table 1). Slightly increased plasma levels of alloisoleucine, the endogenously formed L-isoleucine diastereomer which is pathognomonic for MSUD [37], were still present in cases 1 and 3, and at times with catabolic stress also in case 2. Post OLT, no further metabolic derangement was observed in any of the patients.

In case 1, in vivo BCOA-DH activity after OLT was assessed by different approaches. In Table 2, the results are compared to those in a patient with very mild form of MSUD. The main characteristics of BCAA metabolism in this OLT patient were: 1) on a normal protein diet, plasma BCAA were consistently two- to threefold elevated; 2) the L-alloisoleucine/L-isoleucine ratio in plasma remained slightly above normal. This ratio has been shown to correlate inversely with whole body residual BCOA-DH activity [37]; 3) the metabolic clearance rate in oral L-alloisoleucine loading tests is an adequate parameter for ranking MSUD patients with respect to their residual in vivo BCOA-DH activity [24]. When this test was performed in case 1, the plasma half-life of L-alloisoleucine was within the normal range and was significantly lower than in the mild MSUD variant; 4) in addition, when whole body L-leucine oxidation was assessed by stable isotope techniques [23], the in vivo leucine oxidation rate in case 1 was within the normal range.

These observations clearly show that liver transplantation does not lead to a complete correction of BCAA metabolism in classical MSUD. However, OLT induced an increase in whole body BCOA-DH activity to at least the level of a very mild MSUD variant. Full metabolic correction by OLT is presumably unlikely to be achieved because oxidative BCAA disposal in man is not confined to liver tissue. In healthy subjects, significant amounts of BCOA are oxidised by skeletal muscle, kidney and other organs, which are still enzyme deficient in the MSUD patient after OLT.

Table 1 Reported plasma BCAA levels in classical MSUD patients after OLT

Plasma concentration ($\mu mol \times l^{-1}$)	OLT patients on unrestricted protein intake			Healthy subjects
	Case 1	Case 2	Case 3	
Leucine	235–260	150–200	260 ± 80	134 ± 23
Alloisoleucine	13–19	[a]	< 20	2.0 ± 0.5

[a] Detectable during metabolic stress

Is OLT an option in the management of classical MSUD?

In disorders of BCAA metabolism such as methylmalonic and propionic acidaemia, both dietary management and monitoring of therapy are extremely difficult. Even with the most aggressive treatment, severe complications and permanent organ damage as basal

Table 2 Characteristics of BCAA metabolism in classical MSUD after OLT compared to a mild variant form. *n.d.* not detectable

	Patients on unrestricted protein intake	Healthy subjects	
	Case 1 (OLT)	NA[a] (mild variant)	
Plasma levels:			
BCAA and BCOA	2–3-fold increased	2–3-fold increased	Control range
Allo/isoleucine ratio	0.09 ± 0.02	0.09 ± 0.04	0.03 ± 0.01
In vivo metabolic fluxes[b]			
Alloisoleucine clearance (plasma half-life time, h)	10.3	30.2	10.3 ± 2.1
[^{13}C]Leucine oxidation ($^{13}CO_2$ exhalation, % of dose)	19.5	n.d.	18.9 ± 3.6

[a] 19% residual in vitro activity of BCOA-DH [37]
[b] In oral loading tests with L-alloisoleucine (580 μmol/kg [24]) and L-[1-^{13}C]leucine (38 μmol/kg [23])

ganglia necrosis, chronic renal impairment and cardiomyopathy cannot be totally prevented [5]. In these disorders, liver transplantation leads to an increase in the whole body activity of the deficient enzyme and the phenotype is altered from a severe to a mild form.

Among the disorders of BCAA metabolism, MSUD is comparatively easily treatable with a potentially favourable outcome [3]. In MSUD patients receiving OLT, the very restrictive dietary regimen could be stopped but was replaced by an equally strict monitoring of the immunosuppressive management. Thus, OLT may be unable to reduce the (psychosocial) stress, which is generally associated with a chronic metabolic disorder. In addition, sociocultural conflicts may ensue the organ replacement per se (as in the family of case 1 [19]). Based on these considerations, OLT for correction of disorders in BCAA metabolism is least an option in MSUD.

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