Classic Article

Branched-Chain Amino Acids in Patients With Hepatic Encephalopathy

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ABSTRACT: Hospitalized patients with hepatic insufficiency often suffer from severe catabolic states and are in urgent need of nutrition support during their acute illness. Protein intolerance, however, remains a significant problem with respect to the provision of adequate nutrition, either enterally or parenterally. The following report is an anecdotal series of 63 consecutive patients in a large urban hospital treated prospectively with nutrition support using a prototype high branched-chain amino acid solution (FO80) given by technique of total parenteral nutrition (TPN) by the subclavian or internal jugular route with hypertonic dextrose. Sixty-three patients, of which 42 had chronic liver disease (cirrhosis) with acute decompensation and 17 with acute hepatic injury and four with hepatorenal syndrome, are the subject of this report. All required IV nutrition support and were either intolerant to commercially available parenteral nutrition solutions or were in hepatic encephalopathy at the time they were initially seen. The cirrhotic patients had been hospitalized for a mean of 14.5 ± 1.9 days before therapy, had a mean bilirubin of 13 mg/100 mL, and had been in coma for 4.8 ± 0.7 days despite standard therapy. Patients with acute hepatitis had been in the hospital for 16.2 ± 4.1 day before therapy, had a mean bilirubin of 25 mg/100 mL, and had been in coma 5.2 ± 1.6 days before therapy. Routine tests of liver function, blood chemistries, amino acids, EEGs, and complex neurologic testing including Reitan trailmaking tests were used in the evaluation of these patients. Up to 120 g of synthetic amino acid solution with hypertonic dextrose was tolerated in these patients with improvement noted in encephalopathy of at least one grade in 87% of the patients with cirrhosis and 75% of the patients with hepatitis. Nitrogen balance was achieved when 75 to 80 g of synthetic amino acids were administered. Survival was 45% in the cirrhotic group and 47% in the acute hepatitis group. Encephalopathy appeared to correlate with individual amino acids differentially in the various groups and with the ratio between the aromatic and the branched-chain amino acids. Ammonia did not correlate with either the degree of encephalopathy or improvement therefrom. In 24 patients therapy for hepatic encephalopathy was limited to infusion of the branched-chain enriched amino acid solution only, with wake-up in 66% of this group. The results strongly suggest that in protein intolerant patients requiring nutrition support, infusion with branched-chain enriched amino acid solutions is well tolerated with either no worsening of or improvement in hepatic encephalopathy coincident with the achievement of nitrogen equilibrium and adequate nutrition support. (Freund H, Dienstag J, Lehrich J, et al. Infusion of branched-chain amino acid solution in patients with hepatic encephalopathy. Ann Surg 196:209–220, 1982)

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Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric disorder that develops in patients with acute and chronic liver disease. Patients with HE may show alterations in consciousness, psychomotor, cognitive, and behavioral functions. Based on the level of alteration of these functions, the severity of HE is classified in clinical grades ranging from I–IV, with grade I associated with mild cognitive dysfunction to grade IV as the most advanced stage associated with coma.[1] Several theories have been proposed to explain the pathogenesis of HE, but none of these theories has been clearly established. The theories include γ-amino butyric acid neuroinhibition; amino acid imbalance; ammonia, sulfur-containing amino acid (mercaptans), short- and medium-chain fatty acid, and aromatic amino acid (AAA) neurotoxicity; and zinc deficiency. The treatment of HE consists primarily of identifying and correcting the precipitating factors and lowering ammonia levels. Lowering serum ammonia levels is accomplished by the administration of laxatives (eg, lactulose) to reduce ammonia absorption from the intestines, oral antibiotics (eg, neomycin) to reduce ammonia production by colonic bacteria, and a low-protein diet to minimize ammonia production and avoid excess AAA intake.[1–2] The use of branched-chain amino acids

(BCAA) in the treatment of HE, however, remains a subject of controversy. This review focuses on the role of IV BCAA-enriched formulas in the treatment of acute HE. The role of oral BCAA formulas in the treatment and prevention of chronic HE has been thoroughly reviewed elsewhere.[3]

Amino Acid Imbalance in Patients With Hepatic Failure

Malnutrition is a common finding in patients with liver disease and correlates with increased morbidity and mortality.[4] The prevalence of protein-energy malnutrition has been reported in 27% to 87% of patients with liver cirrhosis.[5] Hypercatabolism during liver disease, along with dietary protein restriction, can lead to protein malnutrition and negative nitrogen balance. Regardless of the patient's nutritional status, amino acid imbalance is a common finding in patients with hepatic failure. Patients with hepatic failure show increased plasma concentrations of AAAs (phenylalanine, tyrosine, tryptophan) and methionine and decreased plasma concentrations of BCAAs (leucine, isoleucine, valine).[6] This observation has led to the hypothesis that amino acid imbalance may contribute to HE.

The low plasma concentrations of BCAAs in patients with hepatic failure could be the result of increased degradation of BCAAs caused by skeletal muscle breakdown during catabolism, reduced protein intake, or as a possible result of hyperammonemia-induced increased BCAA use. On the other hand, the increase in plasma AAA concentrations is due in part to decreased liver function, because the liver is the primary site for AAA metabolism.[7] It is hypothesized that alterations in plasma amino acid concentrations would also affect the amino acid levels in the brain. In patients with hepatic failure, the decreased plasma molar BCAA:AAA ratio could favor the transport of AAAs into the brain as they compete for the same carrier across the blood-brain barrier. This transport is further facilitated by the increased blood-brain barrier permeability as a consequence of hepatic failure, which leads to the accumulation of AAAs in the central nervous system. Based on the theory of "false neurotransmitters," excess tyrosine in the brain is converted to octopamine, and phenylalanine is converted to phenylethanolamine.[8] The newly formed octopamine and phenylethanolamine have been referred to as "false neurotransmitters." The way "false neurotransmitters" may precipitate HE is by either replacing the normal neurotransmitters (eg, dopamine and norepinephrine) at central nerve endings or by competing for normal synaptic transmission.[1,9] If this theory holds true, then changes in the plasma BCAA:AAA ratio would be expected to correlate with the degree of HE.

As such, Fischer et al[10] first used the plasma molar ratio of BCAA:AAA ratio (valine + leucine + isoleucine:phenylalanine + tyrosine) as a marker of the degree of HE. A ratio of 3 to 3.5:1 is considered normal, whereas a ratio ≤ 1 correlates with HE. Therefore, if HE correlates with abnormalities in plasma amino acid concentrations, then normalization of plasma amino acids with an exogenous source of a high-BCAA, low-AAA formula might improve HE while allowing adequate protein intake to achieve nitrogen balance.[7] Because BCAAs are essential amino acids, they cannot be synthesized in the body and thus need to be supplemented from an exogenous source. As such, using a BCAA-enriched formula is based on the hypothesis of amino acid imbalance, with the aim of correcting the plasma BCAA:AAA ratio and possibly treating or preventing HE.

IV BCAAs and HE

The original "hypothesis" of Fischer and Baldessarini[11] provided the initial concept linking the formation of "false neurotransmitters" and amino acid imbalance to HE in patients with liver disease. Since then, clinical studies have emerged to evaluate the role of IV and oral BCAA formulas in patients with acute and chronic HE. These studies have primarily focused on three treatment outcomes: (1) improvement of HE; (2) improvement of the nutritional status; and (3) effect on the survival of patients with liver disease.[12]

The paper by Freund et al,[13] published in 1982, explored the effects of IV BCAAs on recovery from HE, amino acid balance, and nutritional status of patients with liver disease. This was a prospective uncontrolled trial of 63 patients with liver disease who had HE (grade $>$ I) or had intolerance to conventional amino acid formulas, and who required parenteral nutrition (PN). Patients were divided into three groups: group I included 42 patients with chronic liver disease and cirrhosis with acute HE or coma; group II included 17 patients with acute hepatitis; and group III included 4 patients with hepatorenal syndrome. All patients received a high-BCAA, low-AAA solution as part of their dextrose-containing PN regimen. PN provided a maximum of 120 g/d of amino acids and 3000 kcal/d. BCAAs provided 35% of the total amino acids in the specialized formula. Of the 63 patients included in the study, 24 patients did not receive any other treatments for HE (ie, neomycin, lactulose, or cathartics) other than BCAAs. The mean duration of patient treatment was 13 $\pm$ 1 days in group I, 13.2 $\pm$ 3.8 days in group II, and 17.2 $\pm$ 11.3 days in group III. Routine testing included blood chemistries, liver function tests, plasma amino acids and ammonia levels, and neurologic testing. Results of this study showed a significant correlation between plasma BCAA:AAA ratio and the degree of HE (group I: $p < .02$; group II: $p < .002$). After treatment with the specialized amino acid formula, there was a significant increase from baseline in the BCAA:AAA ratio in group I patients ($p < .001$), but the increase in the

ratio in group II patients was not statistically significant. Nitrogen balance significantly correlated with the BCAA:AAA ratio and the amount of nitrogen intake (group I: $p < .001$; group II: $p < .01$). The amounts of amino acids delivered to patients ranged from 60 to 120 g/d and were well tolerated. Nitrogen balance was achieved with amino acid intake of 75 to 80 g/d. There was also a significant linear correlation between daily BCAA intake and nitrogen balance. After 3 days of treatment, HE improved in 56% and 25% in group I and II, respectively. Survival rate was similar in group I (45%) and group II (47%), but was lower in group III (25%). For the 24 patients who received the BCAAs and dextrose only without other treatment modality, 66% of them had improvement in HE with a 50% survival rate. The study concluded that a high-BCAA, low-AAA IV formula corrects plasma amino acid imbalances, achieves nitrogen balance equilibrium, and may improve HE.[13] However, limitations to this study are several and include the lack of randomization, absence of a control group, and absence of blinding to treatment. These limitations prohibit drawing firm conclusions as to the role of BCAAs in patients with severe liver disease. Thus, prospective, randomized, double-blind studies were still needed to confirm the results of this study.

Since the publication of the study by Freund et al,[13] several clinical studies evaluated the role of IV BCAAs in the treatment of acute HE.[14–20] A meta-analysis[21] and a clinical critique of studies[22] were published at about the same time in 1989, but reached opposing conclusions as to the role of BCAAs in patients with liver disease. The 2 papers further raised the debate about the role of BCAAs and the authors took sides in defending their points.

Naylor et al[21] conducted a meta-analysis that included 9 clinical studies[14,15,18,23–28] to evaluate the role of IV BCAAs on mental recovery and survival of patients with acute HE. The meta-analysis included 6 completed randomized controlled studies,[14,15,18,23,27,28] 2 randomized controlled studies in abstract format,[25,26] and 1 study that did not have a randomized controlled design.[24] Using different ways of data aggregation, the authors concluded that IV BCAA formulas significantly improve recovery from HE and perhaps reduce mortality. The authors acknowledged some of the study limitations and cautioned that IV BCAAs could not be recommended for routine use over conventional therapies, and that there is a need for larger randomized, controlled studies with longer follow-up times.[21] Nonetheless, critics of the meta-analysis were numerous, underscoring the validity of the positive conclusions derived from the meta-analysis. The cited limitations addressed the heterogeneity of studies included in the meta-analysis, the type of control therapy, the wide variation in patient selection, the differences in duration of therapy, the amounts of BCAAs used, and the differences in study endpoints.[29] Other critics addressed the methods of literature retrieval and combination of data, discrepancies in data abstraction, the inclusion of data form abstracts and preliminary reports, and the method used for data analysis.[30–34]

Eriksson and Conn critically reviewed and analyzed the strengths and weaknesses of studies that addressed the role of BCAAs in HE. The 7 randomized, controlled studies included in their review[14–19,35] were not all the same as those included in the meta-analysis by Naylor et al.[21] Eriksson and Conn grouped the studies into different categories relative to the role of BCAA in acute HE, chronic HE, subclinical HE, and their effect on nitrogen metabolism. As stated in the review,[22] data from the 2 studies that compared BCAAs with glucose[15,35] and from the 1 study that compared BCAAs with standard amino acids[17] showed no statistically significant difference on HE and mortality between the treatment and control groups. None of the 4 studies that compared BCAAs with either lactulose[14,16] or neomycin[18,19] reported significant differences in improvement of HE or mortality. As such, the reviewers concluded that "BCAA therapy, whether pure or combined with other amino acids, irrespective of the amount administered, does not appear to affect significantly the outcome of patients with acute HE."[22] Even if some studies have shown that BCAAs may be at least as effective as conventional therapy, the positive outcome of BCAA therapy has not been replicated in other studies. Also, BCAAs have not shown to be superior to standard amino acids in improving acute HE.

Conclusion

Over 30 years of research have passed and the "false neurotransmitter" hypothesis has not been clearly proven, nor has the debate about the role of BCAAs in HE been settled. The limitations of the available studies addressing the role of BCAAs include differences in the types, amounts, and composition of BCAAs, and variations in outcome measurements and quality of study designs. Although some investigators' personal experience favors the use of BCAAs, the lack of convincing scientific evidence supporting the effectiveness of BCAA formulas has limited their routine use. Currently, 1 specialized IV amino acid formula (HepatAmine, B. Braun, Bethlehem, PA) is marketed in the United States for patients with HE. This specialized formula contains no tyrosine and provides BCAA at about 35% of total amino acids. As for the role of oral BCAAs in chronic HE, recommendations are to limit their use only to patients who are intolerant to dietary proteins, especially patients with advanced cirrhosis.[3,22] A consensus review in 1997 by the European Society of Parenteral and Enteral Nutrition (E.S.P.E.N) concluded that even if IV BCAAs may have an effect on the patient's mental state, although the improvement may not necessarily be the result of nutrition alone, they have no effect on

patient survival. However, the consensus recommended the use of IV BCAA formulas in patients receiving PN with advanced grade III–IV HE.[36] The Practice Guidelines published by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) state that "there is no consensus concerning the use of BCAA-enriched supplements in the treatment of acute hepatic encephalopathy," and that the "use of BCAA-enriched diets or specialized nutrition support formulas is only indicated in chronic encephalopathy unresponsive to pharmacotherapy."[37]

In summary, BCAA-enriched formulas have not shown significant advantage over standard amino acid formulas and are more costly. Other precipitating factors of HE should be ruled out before considering the patient protein intolerant. During the acute phase of HE, temporary protein restriction to 0.6 to 0.8 g/kg per day is recommended. Except in the minority of protein-intolerant patients, normal protein intake can be resumed in most cirrhotic patients after the resolution of the acute episode of HE to avoid protein malnutrition.

References

1. Gerber T, Schomerus H. Hepatic encephalopathy in liver cirrhosis: Pathogenesis, diagnosis and management. Drugs 60:1353–1370, 2000
2. Ong JP, Mullen KD. Hepatic encephalopathy. Eur J Gastroenterol Hepatol 13:325–334, 2001
3. Fabbri A, Magrini N, Bianchi G, et al. Overview of randomized clinical trials of oral branched-chain amino acid treatment in chronic hepatic encephalopathy. JPEN 20:159–164, 1996
4. Lochs H, Plauth M. Liver cirrhosis: Rationale and modalities for nutritional support-the European Society of Parenteral and Enteral Nutrition consensus and beyond. Curr Opin Clin Nutr Metab Care 2:345–349, 1999
5. McCullough AJ, Bugianesi E. Protein-calorie malnutrition and the etiology of cirrhosis. Am J Gastroenterol 92:734–738, 1997
6. Fischer JE, Yoshimura N, Aguirre A, et al. Plasma amino acids in patients with hepatic encephalopathy. Effects of amino acids infusion. Am J Surg 127:40–47, 1974
7. James JH. Branched chain amino acids in hepatic encephalopathy. Am J Surg 183:424–429, 2002
8. Silk DB. Branched chain amino acids in liver disease: Fact or fantasy? Gut 27(Suppl 1):103–110, 1986
9. Alexander WF, Spindel E, Harty RF, et al. The usefulness of branched chain amino acids in patients with acute or chronic hepatic encephalopathy. Am J Gastroenterol 84:91–96, 1989
10. Fischer JE, Rosen HM, Ebeid AM, et al. The effect of normalization of plasma amino acids on hepatic encephalopathy in man. Surgery 80:77–91, 1976
11. Fischer JE, Baldessarini RJ. False neurotransmitters and hepatic failure. Lancet 2:75–80, 1971
12. Marchesini G, Bianchi G, Rossi B, et al. Nutritional treatment with branched-chain amino acids in advanced liver cirrhosis. J Gastroenterol 35(Suppl 12):7–12, 2000
13. Freund H, Dienstag J, Lehrich J, et al. Infusion of branched-chain amino acid solution in patients with hepatic encephalopathy. Ann Surg 196:209–220, 1982
14. Rossi-Fanelli F, Riggio O, Cangiano C, et al. Branched chain amino acids vs lactulose in the treatment of hepatic coma: A controlled study. Dig Dis Sci 27:929–935, 1982
15. Wahren J, Denis J, Desurmont P, et al. Is intravenous administration of branched chain amino acids effective in the treatment of hepatic encephalopathy? A multicenter study. Hepatology 3:475–480, 1983
16. Fiaccadori F, Ghinelli F, Pedretti G, et al. Branched-chain enriched amino acid solutions in the treatment of hepatic encephalopathy: A controlled trial. Ital J Gastroenterol 17:5–10, 1985
17. Michel H, Bories P, Aubin JP, et al. Treatment of acute hepatic encephalopathy in cirrhotics with a branched-chain amino acids enriched versus a conventional amino acids mixture. A controlled study of 70 patients. Liver 5:282–289, 1985
18. Cerra FB, Cheung NK, Fischer JE, et al. Disease-specific amino acid infusion (FO80) in hepatic encephalopathy: A prospective, randomized, double-blind, controlled trial. JPEN 9:288–295, 1985
19. Strauss E, dos Santos WR, da Silva EC, et al. Treatment of hepatic encephalopathy: A randomized clinical trial comparing a branched chain enriched amino acid solution to oral neomycin. Nutr Suppl Svcs 6:18–21, 1986
20. Vilstrup H, Gluud C, Hardt F, et al. Branched chain enriched amino acid versus glucose treatment of hepatic encephalopathy. A double-blind study of 65 patients with cirrhosis. J Hepatol 10:291–296, 1990
21. Naylor CD, O'Rourke K, Detsky AS, et al. Parenteral nutrition with branched-chain amino acids in hepatic encephalopathy. A meta-analysis. Gastroenterology 97:1033–1042, 1989
22. Eriksson LS, Conn HO. Branched-chain amino acids in the management of hepatic encephalopathy: An analysis of variants. Hepatology 10:228–246, 1989
23. Fiaccadori F, Ghinelli F, Pelosi G, et al. Selective amino acid solutions in hepatic encephalopathy treatment (a preliminary report). Ric Clin Lab 10:411–422, 1980
24. Rakette S, Fischer M, Reimann HJ, et al. Effect of special amino acid solutions in patients with liver cirrhosis and hepatic encephalopathy. IN Walser M, Williams JR (eds). Metabolism and Clinical Implications of Branched Chain Amino Acids and Ketoacids. Elsevier, North Holland, Amsterdam, 1981, pp 419–425
25. Strauss E, Santos WR, da Silva EC. A randomized controlled clinical trial for the evaluation of the efficacy of an enriched branched chain amino acid solution compared to neomycin in hepatic encephalopathy. Hepatology 3:862, 1983
26. Gluud C, Dejgaard A, Hardt F, et al. Preliminary treatment results with balanced amino acid infusion to patients with hepatic encephalopathy. Scand J Gastroenterol 18(suppl 86):19, 1983
27. Michel H, Pomier-Layrargues G, Aubin JP, et al. Treatment of hepatic encephalopathy by infusion of a modified amino-acid solution: Results of a controlled study in 47 cirrhotic patients. IN Capocaccia L, Fischer JE, Rossi-Fanelli F (eds). Hepatic Encephalopathy in Chronic Liver Failure. Plenum, New York, 1984, pp 301–310
28. Fiaccadori F, Ghinelli F, Pedretti G, et al. Branched chain amino acid enriched solutions in the treatment of hepatic encephalopathy: A controlled trial. IN Capocaccia L, Fischer JE, Rossi-Fanelli F (eds). Hepatic Encephalopathy in Chronic Liver Failure. Plenum, New York, 1984, pp 323–333
29. Berlin JA, Chalmers TC. Meta-analysis of branched-chain amino acids in hepatic encephalopathy. Gastroenterology 97:1043–1045, 1989
30. DerSimonian R. Parenteral nutrition with branched-chain amino acids in hepatic encephalopathy: Meta analysis. Hepatology 11:1083–1084, 1990
31. Ferenci P. Branched-chain amino acids in hepatic encephalopathy. Gastroenterology 98:1395–1396, 1990
32. Koretz RL. Branched-chain amino acids in hepatic encephalopathy. Gastroenterology 99:287–288, 1990
33. Erikkson LS, Conn HO. Branched-chain amino acids in hepatic encephalopathy. Gastroenterology 99:604–607, 1990
34. Gluud C. Branched-chain amino acids for hepatic encephalopathy? Hepatology 13:812–813, 1991
35. Vilstrup H, Gluud C, Hardt F, et al. Branched chain enriched amino acid nutrition does not change the outcome of hepatic coma in patients with cirrhosis of the liver. J Hepatol 1(Suppl 2):347, 1985
36. Plauth M, Merli M, Kondrup J, et al. ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr 16:43–55, 1997
37. A.S.P.E.N. Board of Directors and The Clinical Guidelines Task Force. Specific Guidelines for Disease—Adults. Liver Disease. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. JPEN 26(Suppl):65S–68S, 2002