The effects of branched-chain amino acid-enriched elemental diet in patients with biliary atresia

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Supplemental administrations of ED-H, branched-chain amino acid (BCAA)-enriched elemental diet for hepatic disorder, were performed in 10 postoperative biliary atresia (BA) patients. These patients were exhibiting, more or less, cirrhotic changes. The duration of ED-H administration ranged from 7 months to 3 years. initially, these patients showed lowered molar ratios, Val+Leu+Ile/Phe+Tyr, in plasma aminograms with decreased levels of plasma rapid-turnover proteins. ED-H administration induced a significant increase in molar ratio as well as increases in plasma prealbumin and retinol-binding protein levels. With an improved general status, such as activity level and play performance, there were significant increases both in weight for age and weight for height. No particular deleterious effects were observed throughout the period of ED-H administration.

In conclusion, supplemental ED-H administration can be performed safely with an efficacy in postoperative BA patients who need metabolic/nutritional supports due to abnormal liver functions.

Introduction

In spite of remarkable progress in surgical treatment, little attention has been paid to nutritional/metabolic care of postoperative biliary atresia (BA) patients. Currently, the importance of nutritional management is being emphasized in postoperative BA patients, since many of these patients have been revealed to be malnourished, accompanied with deficiencies in essential fatty acids, fat-soluble vitamins and trace elements[1,2]. Our previous study demonstrated certain postoperative BA patients exhibiting abnormal plasma amino acids profiles reflected by decreased levels of branched-chain amino acids (BCAA) and increased levels of aromatic amino acids (AAA)[3]. These patients were also exhibiting lowered levels of plasma proteins[3].

In adult cirrhotic patients, the administration of a BCAA-enriched formula diet has proven nutritionally effective with associated improvements in hepatic encephalopathy.[4–11] . In this study, supplemental administrations of ED-H, an elemental diet for the adult patients with hepatic disorder, were performed in 10 postoperative BA patients. Most patients were jaundiced, accompanied by liver dysfunctin. They also showed molar ratios Val+Leu+Ile/Phe+Tyr (B/A : BCAA/AAA) below 2.0 in plasma aminograms and lowered levels of prealbumin and/or retinal-binding protein.

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Table 1. Nutritional composition of ED-P and ED-H (1 pack).

	ED-P	ED-H
Amino acid (g)	9.8	11.2
Total N (g)	1.4	1.8
Dextrin (g)	62.0	59.5
Fat (g)	2.8	2.8
Calorie (Cal)	312	309
Cal/N	223	176
Amino acids (%)		
ILE	5.29	15.44
LEU	10.24	18.94
VAL	5.47	14.22
LYS	7.74	6.96
MET	1.62	1.04
PHE	3.16	1.04
THR	5.06	3.89
TRP	1.90	0.50
ALA	7.06	8.73
ARG	9.79	15.51
ASP	4.26	—
CYS	2.20	—
GLN	7.62	—
GLY	2.31	3.84
HIS	2.86	2.74
PRO	9.95	4.66
SER	9.01	2.29
TYR	4.46	—
EAA	40.48	62.23
NEAA	59.52	37.77
BCAA	21.00	48.80

ED-P: conventional elemental diet for Pediatric use.
ED-H: elemental diet for hepatic disease

Patients and methods

The composition of ED-H is shown in Table 1, as is the composition of the standard formula of an elemental diet (ED-P) which was devised for pediatric use and commonly used in Japan. ED-H is an admixture of dextrin, fat and an amino acid mixture composed of 14 kinds of free amino acids, packed in powder form in a bag containing 80 g, an equivalent of 309 kcal. As to the amino acid composition, ED-H has a higher BCAA content (48.0%) and Arg, with a lower content in Phe and Met than ED-P. Asp, Cys, Gln and Tyr are not contained in ED-H.

Ten postoperative BA patients aged 6 months to 10 years, 8 females and 2 males, were admitted to this study. All patients initially had a Kasai hepatic portoenterostomy performed at the average age of 2 months. Adequate bile excretion was obtained in 5 patients (cases 1, 2, 3, 5 and 10) postoperatively with resolution of jaundice. The remaining patients exhibited inadequate bile excretion with persistent jaundice, represented by the levels of serum total bilirubin over 5.0 mg/dl. No patients were noted to have apparent edema and/or ascites clinically before the trial.

Individual characteristics are shown in Table 2. Before ED-H administration, the levels of B/A were noted to be less than 2.0 in all patients. Finally, 8 patients survived and 2 patients, cases 4 and 8, died of hepatic failure after discontinuation of ED-H administration.

ED-H was administered orally in all but one patient, case 8, in whom it was administered continuously for 3 weeks by tube-jejunostomy due to diarrhea. Administration doses were from 16 to 71 cal kg BW/day, averaging 50 cal kg BW, and with an amino acid content of 0.6 – 2.6 g/kg BW, averaging 1.8 g/kg BW. The duration was 7 months to 3 years, averaging 1.5 years. The individual dose and duration in each BA patient is shown in Table 3. ED-H was administered supplementally with regular diets in 5 patients and with ED-P in the other 5 patients. The following clinical features and the biochemical data were recorded at an interval of 1 month on an outpatient basis. Certain parameters were obtained after 6 months of ED-H administration and compared to those obtained prior to its administration. The clinical features were evaluated by the authors referring to the parents' comments. Anthropometric measures were compared with the standard data for Japanese which were presented in 1980 by the Japanese Ministry of Health and Welfare. Blood samples were obtained in the fasting state in the morning every month. As laboratory findings, the serum levels of GOT, GPT, gamma-GTP, alkaline phosphatase, total bilirubin, direct bilirubin, total bile acid, albumin, and electrolytes were measured. Plasma amino acids and rapid-turnover proteins (RTPs), transferrin, prealbumin, and retinol-binding protein, were determined by column chromatography with an amino acid auto-analyzer, Hitachi Co, Model 835, and an immuno-diffusion method respectively.

Prior to admission to the trial, informed consent was obtained from every patient and/or family. Statistical analysis was performed by paired *t*-tests. The level of statistical significance was taken at $P<0.05$.

Table 3. Individual methods of ED-H administration.

Case	Dose (cal/kg/day)	Duration	Basal diets
1	16	1 Y 1 M	Regular diet
2	39	3 Y	Regular diet
3	36	1 Y 10 M	Regular diet
4	64	2 Y 6 M	Regular diet
5	45	1 Y 10 M	Regular diet
6	62	7 M	ED-P → Weanling diet
7	71	2 Y 4 M	ED-P → Weanling diet
8	62	2 Y 5 M	ED-P → Weanling diet
9	38	7 M	ED-P → Weanling diet
10	63	8 M	ED-P → Weanling diet

Results

Clinical features

ED-H administrations were well tolerated by all patients. Though diarrhea was noted in one patient, case 8, during the course, it was transient and disappeared when continuous feeding by tube-jejunostomy was performed. In six patients, cases 2, 3, 4, 5, 7, 8, general status, such as activity level and play performance, improved remarkably, especially in case 2. While the patient had complained of severe general fatigue with advanced intrapulmonary A-V shunt, she was able to go upstairs following ED-H administration.

Table 2. Individual characteristics of 10 biliary atresia patients.

	Anthropometry					Liver Tests					Protein levels			
Case	Age	BW (kg)	Wt/Age (%)	Ht/Age (%)	Wt/Ht (%)	T B (mg/dl)	GOT (U/l)	GOT (U/l)	r–GTP (U/l)	B/A	Alb (g/dl)	TF (mg/dl)	PA (mg/dl)	RBP (mg/dl)
1	10Y 9M	37.0	102	101	98	1.3	185	148	869	1.62	4.0	233	10.9	1.2
2	6Y11M	15.5	70	92	83	2.1	136	130	791	1.82	3.8	420	9.5	1.0
3	4Y 1M	16.5	106	97	122	2.5	64	40	169	1.13	3.7	275	9.5	1.6
4	4Y 1M	14.0	84	91	99	8.0	284	222	158	1.22	3.8	362	10.5	0.7
5	2Y 7M	13.2	108	100	110	2.0	256	174	646	1.85	3.9	320	9.5	1.3
6	1Y 8M	9.7	95	94	103	6.2	211	232	1354	0.92	4.3	324	24.9	3.1
7	8M	8.5	109	103	104	5.1	178	84	336	1.20	3.3	260	7.0	1.1
8	7M	6.5	82	95	92	8.0	240	96	368	1.06	3.6	230	7.0	1.4
9	7M	8.0	107	103	99	9.0	324	168	440	1.14	3.6	200	3.5	0.4
10	6M	6.5	87	102	83	0.9	139	111	920	1.93	4.2	233	9.6	1.8

B/A:BCAA/AAA = VAL+LEU+ILE/PHE+TYR; TF, transferrin; PA, prealbumin; RBP, retinol-binding protein.

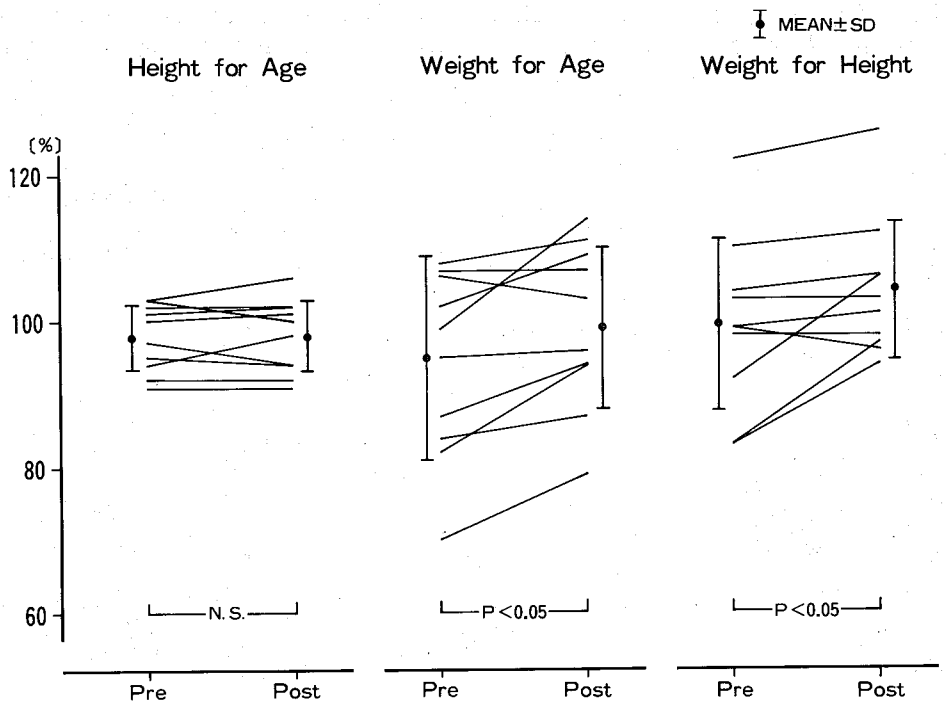

Figure 1. Changes in anthropometric measures following Ed-H administration.

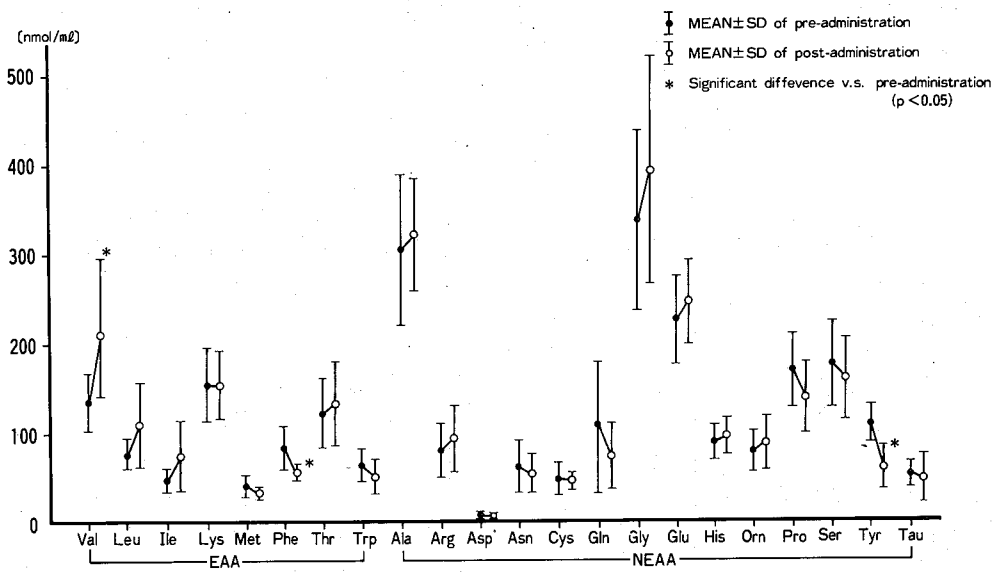

Figure 2. Changes in plasma amino acids following ED-H administration.

Table 4. Comparison of biochemical findings between pre- and post-administration of ED-H.

	Total bilirubin (mg/dl)	Direct bilirubin (mg/dl)	GOT (U/l)	GPT (U/l)	ALP (U/l)	T-GTP (U/l)	Total bile acid (μmol/l)
Pre-administration	4.5±3.1	2.6±2.0	202±78	141±61	1373±582	605±382	101±44
Post-administration	6.6±5.8	3.8±3.4	192±73	131±64	1208±409	442±329	127±65
Statistical analysis	N S	N S	N S	N S	N S	$P<0.05$	N S

Statistical analysis was performed by paired-t test. The level of statistical significance was taken at $P<0.05$.

Anthropometric measures (Figure 1)

Both weight-for-age and weight-for-height showed significant increases whereas height-for-age did not. In weight-for-age, four of the patients exhibited under 90% of standard weight before the trial. Two of them remained the same after the trial. In weight-for-height, two patients were below 90%, whereas none were below that level after the trial.

Laboratory findings

As regards liver tests, no examinations except gamma-GTP showed significant changes during 6 months fol-

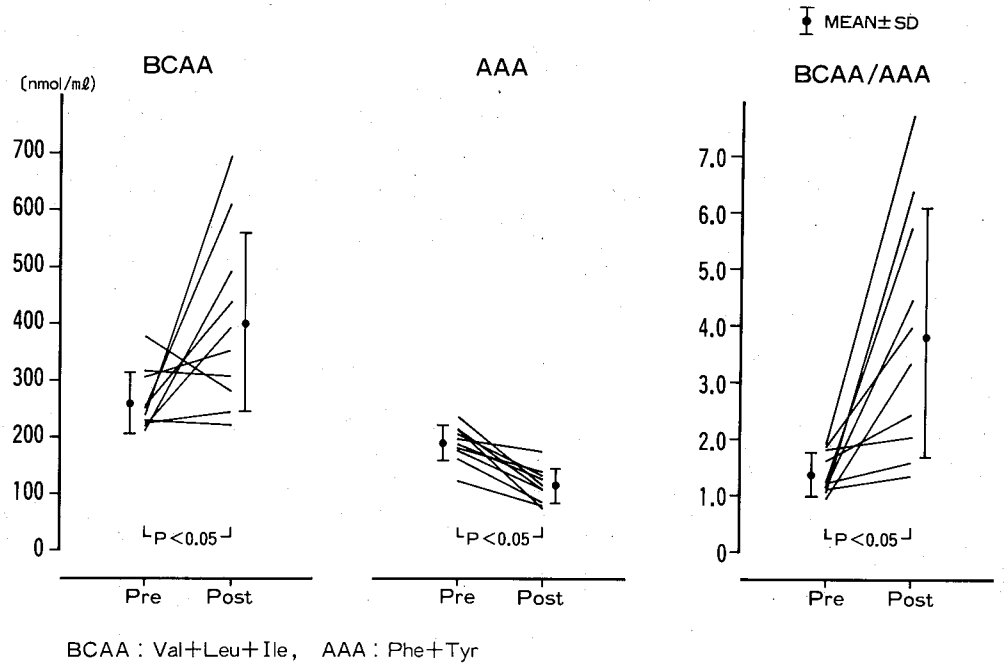

Figure 3. Changes in plasma BCAA, AAA and BCAA/AAA following ED-H administration. BCAA = Val+Leu+Ile, AAA = Phe + Tyr.

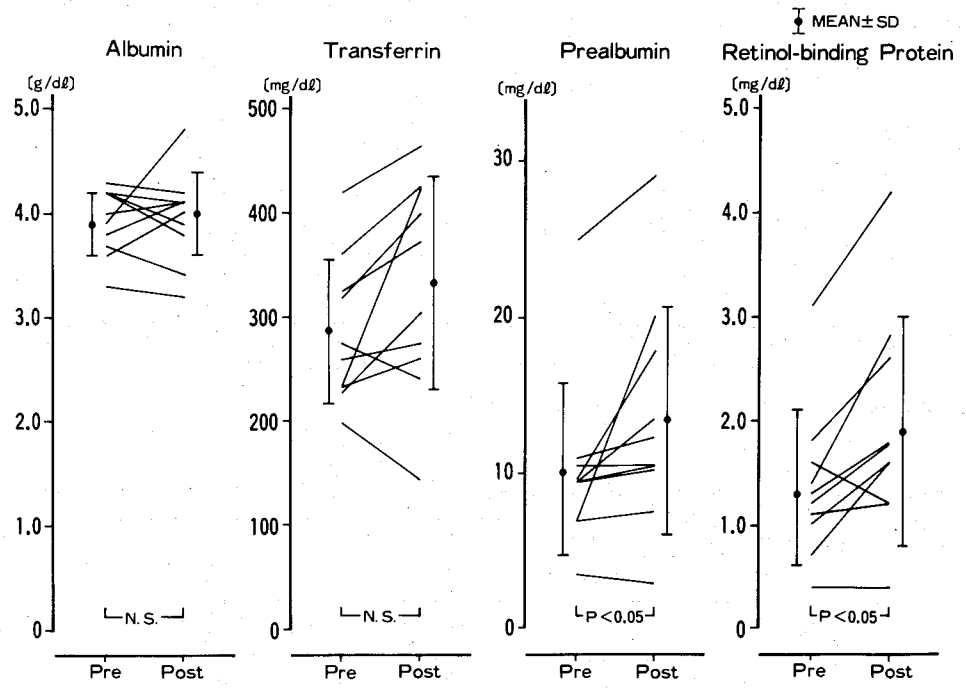

Figure 4. Changes in serum albumin and plasma rapid-turnover proteins following ED-H administration.

lowing ED-H administration (Table 4). Abnormalities in serum electrolytes were not noted. Figure 2 shows the change of plasma aminogram before and 6 months after ED-H administration. A significant increase in valine and significant decreases both in phenylalanine and tyrosine were noted in the trial. As is seen in Figure 3, Val+Lau+Ile (BCAA) increased significantly, whereas Phe+Tyr (AAA) decreased significantly. As a consequence of these changes, B/A increased significantly. Figure 4 shows changes of serum albumin and plasma RTPs following ED-H administration. Prealbumin and retinol-binding protein levels increased significantly, whereas the changes both in albumin and transferrin were not significant.

Discussion

Since the introduction of Kasai hepatic portoenterostomy, great improvement has been obtained in the treatment of BA[12]. Recently, attention has been paid to liver dysfunction in postoperative BA patients since many of them, even in jaundice-free patients, have been reported to develop, more or less, metabolic/nutritional abnormalities[13,14]. On the other hand, the life span of the patients is being extended, even in jaundiced patients with advanced liver dysfunction, due to progress in a variety of managements including nutritional/metabolic supports. Accordingly, one of the current means for improving the quality of life in the postoperative BA patient is to correct their metabolic/nutritional abnormalities, which are usually accompanied with protein-energy malnutrition.

BCAAs are oxidized in skeletal muscles rather than in the liver, because the majority of their transaminases are located in skeletal muscles[15]. The decreased BCAA levels, the increased AAA levels and the ensuing lowering of the B/A ratio are reported to be the characteristic pattern of liver insufficiency, though the precise mechanisms of those changes have not been elucidated. Fischer showed that the B/A ratio is significantly reduced in patients with hepatic encephalopathy[16]. Morgan reported that lowering of the B/A ratio appeared to be secondary to liver damages[17]. Merli suggested that malnutrition might contribute to decreased BCAA levels and increased phenylalanine levels in patients with liver cirrhosis[18]. We reported previously that BA patients had shown decreased BCAA levels, increased AAA levels and methionine, and a lowering of the B/A ratio in plasma aminogram[3]. Weisdorf also reported similar abnormalities with a significant B/A ratio decrease in BA patients as we reported[13].

Feeding with BCAA-enriched amino acid mixture was initially proposed as a specific therapy for patients with hepatic encephalopathy[16]. However, as the clinical studies on abnormal amino acid metabolism in several critical conditions have been performed by a number of investigators, its efficacy and unique metabolic characteristics are now generally accepted[19]. In addition, it is suggested that leucine has the function of stimulating protein synthesis and that its alpha-keto analogue has the function of inhibiting protein breakdown[20].

BCAA-enriched elemental diets have reported to have an effect of improving the nutritional state as well as ameliorating hepatic encephalopathy in adult patients with liver insufficiency[6–9]. Oroshi also demonstrated the nutritional effects of ED-H for adult patients with hepatic disorder in a Japanese multicenter study[21].

We first tried to assess the efficacy of orally administered BCAA-enriched elemental diet (ED-H) in pediatric cases with liver cirrhosis. Our trial was uncontrolled and did not have cross-over design. However, our data with oral supplemental administration of BCAA-enriched elemental diet for BA patients showed an effect on normalizing their plasma aminogram reflected by an elevation of the B/A ratio. Moreover, significant increases in prealbumn and retinol-binding protein were noted. Whereas it is unlikely that liver functions of BA patients have improved during these 6 months judging from the results of liver tests, the changes of RTPs could have reflected an improvement of nutritional state in those patients. Although RTPs are believed to be more sensitive nutritional parameters compared to albumin, some arguments can be made that they would not represent nutritional changes over longer periods of time. However, Kato reported, based on the clinical studies with adult cirrhotic patients, that BCAA-enriched nutrient mixture improved albumin synthesis rate without significant changes of plasma albumin level in the analysis of kinetic parameters of albumin metabolism following intravenous injection of ^{131}I-labelled human serum albumin[22]. It can be speculated that BCAA-enriched formulae, such as ED-H, have the possibilities of improving protein metabolism even if an elevation of serum albumin level could not be obtained. As regards anthropometric measures, significant increases both of weight-for-age and weight-for-height were noted without progression of edema and/or ascites. The reason why no significant change was noted in height-for-age might be the dependence on length for evaluation of its effects. From the clinical aspect, we observed apparent improvement in general status such as activity level and play performance, and ameliorated fatiguabilities in some patients. These effects on physical development and clinical findings might be correlated with the changes of plasma aminograms, especially with B/A ratio.

Weisdorf emphasized that manipulation of each amino acid in dietary protein may be helpful in improving amino acid utilization in patients receiving liver transplants[13]. Goulet also suggested the necessity of nutritional evaluation and support before liver transplant[23]. In the future, nutritional support using the BCAA-enriched formula, such as ED-H, could play an important role in the preoperative management of liver transplant.

The data presented in this paper show the possibility that the supplemental administration of ED-H has an efficacy on metabolic/nutritional disorders without apparent deleterious effects in BA patients who show abnormal patterns of plasma aminograms and lowered B/A ratios. However, further studies are needed to investigate the precise mechanisms of the function of this formula.

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肝障害用に開発された分岐鎖アミノ酸を豊富に含む成分栄養食ＥＤ－Ｈを胆道閉鎖症の患児１０例に投与した。これらの患児はいずれも程度の差はあれ、肝硬変を伴っていた。ＥＤ－Ｈは７ヵ月から３年に亘り投与された。投与前、Val+Leu+Ile/Phe+Tyr(Fischer 比)は低く、血漿蛋白（代謝回転の早い）も低値を示した。ＥＤ－Ｈ投与により、Fischer 比、血漿プレアルブミン、レチノール結合蛋白は上昇を示した。これと共に全身状態も改善し、、活動性を増し、身長・体重も有意の増加を認めた。ＥＤ－Ｈ投与期間、特にこれに基ずくと思われる副作用は認めなかった。以上、胆道閉鎖症術後患児において、肝機能が異常を呈し、栄養代謝管理が必要と思われる場合、ＥＤ－Ｈの補食投与は安全且つ有効な治療法になり得ると思われる。

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摘 要

作者用十個膽道閉鎖（ＢＡ）經手術後的肝病患者，補充富含支鍵氨基酸（ＢＣＡＡ）的要素飲食（ＥＤ－Ｈ）。這些病人或多或少有肝硬化改變。要素飲食的補給時間爲七個月到三年。最初，這些病人的纈氨酸十亮氨酸十異亮氨酸與苯丙氨酸十酪氨酸的克分子比率較低，血漿快速轉換蛋白水平下降。要素飲食的補給使克分子比率明顯升高。同時使血漿前白蛋白和視黃醇＿＿結合蛋白水平升高。不論以年齡和身高爲標准，病人体重均有明顯增加。病人一般情況和活動水平和活動效率均有改善。在要素飲食的補給期間，沒有出現特殊的副作用。

作者認爲，因肝功能異常而需要營養，代謝支持的，膽道閉鎖經手術后的病人，補充要素飲食會起到安全和有效的作用。