Nutritional Requirements of Infants and Children with Liver Disease

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Owing to the somewhat unpredictable nature of the normal growing child's appetite and dietary pattern, superimposition of special nutritional requirements by acute and chronic liver disorders often go unmet. Furthermore, when a child is ill, especially if hospitalized and separated from parents, anxieties about his strange environment may often lead to regression to more infantile feeding patterns. Experience has demonstrated that the therapeutic approach to each patient must be individualized (1, 2).

The Stuart growth charts (Fig. 1) may be used for long-range objective assessment of nutritional progress in a sick patient. A child may be unable to resume his former growth rate precisely, but the postillness curve may be adequate even if somewhat below the earlier level. Children who at first glance appear asthenic and undernourished may maintain consistent height and weight channels for prolonged periods. Such objective evidence may in these instances reassure physicians against overemphasis on nutritional needs. Conversely, concern may be generated earlier than might normally arise if a particular child continues to grow at a suboptimal pace and crosses over into lower growth channels.

It is important to impose a minimal number of dietary restrictions on children. A relatively liberal diet and activity program results in more cooperative patients and decreases the number of frustrated parents and doctors. In many instances such programs have no adverse effects on the course of the disease. It is desirable to appraise critically the many loosely contrived dietary regimens that are entrenched in our therapeutic armamentarium.

Infectious Hepatitis

Infectious hepatitis is primarily a disease of children and young adults. The child is typically less ill than an adult with this disease, is more likely to remain anicteric, and rarely develops sequelae. Some degree of steatorrhea is noted in most patients with hepatitis and cholestasis. Fat intolerance in adults has led to the low fat diet regimen. Such restrictive regimens might not be necessary since children with hepatitis have rarely been observed to be affected by normal fat-containing diets after the 1st week of their illness. Recently, Chalmers et al. (4) and our own unit (5) independently compared the effects of a low fat diet with that of a liberal fat-as-tolerated regimen and found that the latter is not associated with any undesirable effects on the acute illness and convalescence, nor does it induce late sequelae (Figs. 2, 3).

An ad libitum fat diet is recommended for children with hepatitis (about 2–3 g/kg body wt). This results in improved protein intake over that which is usual with low fat diets, a factor important in hepatic repair. At least 1.5 g protein/kg body wt is advisable in any child with...
FIG. 1. Growth charts used for plotting weight, height, and head circumference up to 13 years and for female children. Graphs are based on studies of children in Boston of predominantly north European stock. Separate charts are used for male and female children. (Charts reproduced from Stuart and Meredith [3] by permission of the authors. For charts that extend to age 18 see reference 3.)
Liver Disease Associated with Disorders of Bile Secretion

Prolonged and severe obstruction to the flow of bile into the intestinal tract is most commonly associated with anomalies of the extrahepatic biliary system. In patients with complete obstruction, e.g., biliary atresia, surgical correction is possible in about 20% of the cases. However, the eventual salvage rate has rarely exceeded one-third of the corrected cases because of the presence of irreversible biliary cirrhosis (6).

From the nutritional point of view, a major deficit arises from the steatorrhea that follows the virtually total exclusion of bile salts from the bowel lumen. Coefficients of fat absorption in infants with biliary atresia range from 20–65% and the resultant chronic malnutrition contributes to the poor growth and development of these children. Reduced fat intake and dietary supplementation with water-miscible preparations of vitamins A and D result in a reduction of anorexia, less steatorrhea, and an improved sense of well-being, but unfortunately does not improve growth. However, introduction of medium-chain fatty acid triglyceride (MCT) diets with chain lengths of 8–12 carbon atoms partly compensates for the absent bile secretions and permits growth (7). The usual regimen contains 80% of dietary fat in this form with the remaining

Rigid dietary restrictions were widely imposed. However, because of the prolonged cholestasis that accompanies some cases of hepatitis, administration of water-miscible derivatives of the fat-soluble vitamins A, D, and K remains of importance. Dosages of twice the normal basic requirements are usually recommended for all patients (1).

Generally, the other disorders associated with acute hepatocellular damage have nutritional requirements similar to those of infectious hepatitis.

Figure 2. Clinical effects of an ad libitum fat diet (average, 2.3 g/kg) in 42 patients with infectious hepatitis compared with a low-fat diet (average, 1.0 g/kg) in 44 patients. (Source, Silverberg et al. (5) with permission of the publisher.)

Figure 3. Effect on serum transaminases of an ad libitum fat diet (average, 2.3 g/kg) in 42 patients with infectious hepatitis, compared with a low fat diet (average, 1.0 g/kg) in 44 patients. (Source, Silverberg et al. (5) with permission of the publisher.)

hepatitis who is over the age of 6 months. Supplemental multiple vitamins, discussed elsewhere in this symposium, may appear to have been more necessary only when
20% as long-chain fatty acid triglycerides. The use of some long chain triglycerides appears to be important in the growing organism to meet the requirements for certain essential fatty acids, e.g., linoleic acid. Figure 4 shows the dramatic short-term effects of the MCT diet on growth patterns in two patients with complete, irreparable extrahepatic biliary obstruction (unpublished data).

Liver diseases with primary intrahepatic cholestasis, although associated with similar nutritional deficits, are usually benign recurrent disorders, and life expectancy is not adversely affected (8). However, the case fatality ratio is very high in other familial varieties such as Byler disease (9) and in the cases described by Sharp et al. (10), Juberg et al. (11), or Gray and Saunders (12). In all cases, and in particular the more virulent types, defective bile acid secretion results in steatorrhea, and a diet containing fat predominantly of the MCT variety is of some therapeutic value.

Cirrhosis

Juvenile cirrhosis is most commonly of the postnecrotic variety although the specific predisposing liver disease is usually obscure. Chronic persistent disease is rarely a result of clinically apparent acute infectious hepatitis. In only a small number of cases can the cirrhotic condition be definitely assigned to a preexisting chronic metabolic disorder (Table 1). However, regardless of etiology the cirrhotic child is usually malnourished, apathetic, and anorectic.

The recommended diet is essentially the same as for infectious hepatitis. Caloric requirements are usually 50–75% above normal values at each age group. The desirable protein intake of 3–4 g/kg body wt should be drastically curtailed at the first signs of hepatic failure. Simple forms of carbohydrates may be used to make up the calories. Short-term studies with diets containing fat with a high proportion of

![Fig. 4. Treatment of two infants with inoperable biliary atresia, with a diet in which 80% of fat was medium-chain fatty acid triglyceride. Effect on weight and height are noted in patient 1 (O—O—O) and patient 2 (X—-X—X).](https://academic.oup.com/ajcn/article-abstract/23/5/604/4733090)
Metabolic disorders in which liver disease may be prominent

<table>
<thead>
<tr>
<th>Metabolic disorders</th>
<th>Primary biochemical defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Cystic fibrosis</td>
<td>Unknown</td>
</tr>
<tr>
<td>2) Glycogenosis (glycogen storage disease</td>
<td>lactic acid ▶ Glc-6-P04-ase ▶ Glc-PO4 ▶ glucose</td>
</tr>
<tr>
<td>a) <em>Type I</em> (Von Gierke’s)</td>
<td>Lysosomal α-1,4-glucosidase deficiency</td>
</tr>
<tr>
<td>b) <em>Type II</em> (Pompe’s disease)</td>
<td></td>
</tr>
<tr>
<td>c) <em>Type III</em> (debrancher enzyme)</td>
<td>Amylo-1,6-glucosidase ▶ Glc-1-PO4 ▶ Oligo-1,4,4-glucosidase transferase ▶ Phosphorylase ▶ Glc</td>
</tr>
<tr>
<td>d) <em>Type IV</em> (brancher enzyme)</td>
<td>(Glucoyl [1,4])n+1+ UDP ▶ Glc-5-P04 ▶ glycogen</td>
</tr>
<tr>
<td>e) <em>Type VI</em> (hepatic phosphorylase, Her’s disease)</td>
<td>Glycogen ▶ Glc-1-PO4</td>
</tr>
<tr>
<td>f) <em>Type VII</em> (phosphoglucomutase)</td>
<td>Phosphoglucomutase ▶ Glc-1-PO4 ▶ Glc-6-PO4</td>
</tr>
<tr>
<td>g) <em>Type VIII</em> (phosphorylase inactivation)</td>
<td>Phosphorylase (inactive) ▶ phosphorylase (can be activated by glucagon or epinephrine)</td>
</tr>
<tr>
<td>h) <em>Type IX</em> (phosphorylase kinase)</td>
<td>Dephosphorylase ▶ phosphorlase</td>
</tr>
<tr>
<td>3) Wilson’s disease</td>
<td>Unknown</td>
</tr>
<tr>
<td>4) Galactosemia</td>
<td>Gal 1-PO4 + UDP-Glc ▶ UDP-Glc-PO4-unidyl transferase ▶ UDP + Gal + Glc 1-PO4</td>
</tr>
<tr>
<td>5) Hereditary tyrosinemia (tyrosinosis)</td>
<td>p-OH-phenyl pyruvic acid (pHPA) ▶ homogentisic acid</td>
</tr>
<tr>
<td>6) Hereditary fructose intolerance (aldolase deficiency)</td>
<td>Fru-1-PO4 ▶ Fru-1,6-PO4</td>
</tr>
<tr>
<td></td>
<td>Glyceraldehyde + dihydroxyacetone + glyceraldehyde-PO4</td>
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Height, with accompanying delayed sexual maturation in adolescents. These effects are aggravated among those patients on corticosteroid therapy. Growth stunting and sexual infantilism are often of greater concern to parents and patients than is the primary illness. Therapeutic measures are of limited value, and successes appear more to be related to remissions in the disease process than to "specific" maturation therapy. Although anabolic agents used in children have exhibited limited success in promotion of protein synthesis and growth, patients so treated are subjected to an undesirable side effect of these agents, i.e., advancement of bone maturation, which further stunts growth by acceleration of the closure of the epiphyses, in addition to possible aggravation of hepatocellular dysfunction by these drugs.

Hepatic coma is a rare condition in children, but it may develop in acute or chronic disease. One of the fundamental principles of dietary management, to avoid impending encephalopathy, is to limit protein intake in order to minimize pro-
tein catabolism and thus reduce production of toxic nitrogenous substances. Once present, extraordinary measures for correcting the noxious factors leading to coma may be lifesaving among the critically ill patients, i.e., exchange transfusion, extracorporeal hepatic perfusion, and cross-circulation. Carbohydrates, administered orally, by tube, or by the intravenous route, are used as the main source of energy and as protein-sparing agents. Protein intake should be completely avoided for the initial 24–48 hr, followed by gradual increases to 0.5 g/kg body wt. As the patient’s condition improves, this value is slowly increased to 1.0 g/kg. Multiple vitamins are empirically employed using twice the recommended dosages.

Indian Childhood Cirrhosis

Cirrhosis among children between the ages 1 and 5 is so prevalent in the subcontinent of India that it constitutes a major public health problem. A similar, if not identical, disease affects children in Indonesia. Numerous etiological factors have been implicated, but the most plausible is the superimposition of nutritional factors on infectious hepatitis (13). Rigid adherence to a number of local traditional feeding customs complicates efforts at elucidating the possible role of a specific nutritional deficiency or of a toxic factor that might be induced by one of these particular diets. Chronic soil deprivation resulting from centuries of poor fertitigation techniques may contribute to the problems, but this explanation is inconsistent with the widespread similarities of farming practices and the limited regional distribution of cases. Recent interest in aflatoxin, which frequently contaminates stored grains in India, requires further exploration (14).

In contrast to possible implication of a specific nutritional deficiency or to generally poor nutrition as etiologic factors, it is interesting to note that childhood cirrhosis is proportionately relatively common in well-to-do families and is most prevalent in some of the more developed areas of the country, e.g., Madras State. The disease has never been reported among Indian children living in western countries. It is reversible only in its earliest stages, and a wide variety of therapeutic regimens, e.g., adrenal corticosteroids, antimicrobial therapy, and parenteral vitamins, has been used in vain efforts to improve patients with well-established cirrhosis. A single case of advanced degree showed remarkable improvement after the child was brought from India to live with his parents in Canada (unpublished data). No specific changes in his therapy could be credited with this encouraging observation.

Cystic Fibrosis

Cystic fibrosis (CF) is a disease with protein manifestations involving multiple organ systems. The hepatic features vary among a) prolonged neonatal jaundice associated with obstruction of the intrahepatic bile ductules (15); b) fatty liver (16); and c) biliary cirrhosis, which may be subclinical, mild, and focal or may develop into a severe generalized picture with or without portal hypertension (17). The severely cirrhotic patient is relatively uncommon and is often undiagnosed until late childhood or adolescence, suggesting a gradual development of the problem. Virtually all CF patients beyond adolescence show some clinical manifestations of hepatic disease. Perhaps all hepatic lesions and certainly those associated with undernutrition, may be prevented by diligent management of nutritional problems in children with cystic fibrosis.

The recommended diet is high in protein (4–8 g/kg per day), high in carbohydrate, and only moderate in fat. Medium-chain triglyceride replacement of fat permits larger amounts of dietary fat and has resulted in improved growth and weight
gain (18). Water-miscible preparations of the fat-soluble vitamins A and D in daily doses of 10,000–20,000 IU and 800–1,000 IU, respectively, are administered. Supplementary vitamin K and vitamin E may be necessary and are recommended for all patients by some workers (19). Eighty to ninety percent of patients demonstrate moderate to severe pancreatic exocrine insufficiency requiring oral pancreatic enzyme supplementation to be taken with all meals and snacks. If the replacement therapy is adequate it usually results in improved digestion of foods, more normal stools, a reduction of the excessive appetite, which patients usually display, and weight gain. Special dietary variations are necessary when complications develop. Some older patients develop a tendency to intraluminal impaction of inspissated material and may require additional fluids and pancreatic enzymes with a high roughage diet. Under extremely warm climatic conditions, supplementary salt (1–5 g/day) is given to avoid the tendency to heat prostration due to excessive loss of electrolytes in the sweat. The increase in salt intake must be balanced with the possible deleterious effects of heart failure among patients with cor pulmonale.

Glycogenosis

Disorders of glycogen synthesis and glycolysis have been classified into nine different types (see Table 1) (20), and except for the phosphorylase defect of skeletal muscle (McArdle's syndrome), all involve the liver with excessive glycogen deposition often combined with steatosis. Clinically, patients with glucose-6-phosphatase deficiency (type I) and the various phosphorylase defects suffer from recurrent hypoglycemia and this necessitates frequent small meals, which include simple carbohydrates. In young infants this problem may require feeding every 1 or 2 hr. In type I disease, increased concentrations of lactic acid and secondary hyperuricemia add further complications and require careful control. These latter infants must be given milk substitutes since galactose cannot be converted to glucose. In enzyme defects of the brancher (amylo-1,4 → 1,6-transglucosidase) and debrancher (amylo-1,6-glucosidase) types, gluconeogenesis is active and a high protein diet is prescribed for the frequent feedings. Hepatocellular damage, severe enough to result in fibrosis and eventually in cirrhosis, is found only in the latter two forms of glycogenosis. This is particularly true in the brancher enzyme defect, although the pathogenesis of this nutritional type of cirrhosis is not understood (21). In α-l-glucosidase deficiency, hypoglycemia is not a problem and nutritional management rarely modifies the course of this highly fatal disease (22). The multiple enzyme defects reported in some cases (23) are probably due to the absence of a single enzyme, with secondary depression of the activity of the other.

Galactosemia

Children with galactosemia are unable to convert galactose to glucose because of a congenital defect of the enzyme galactose-1-phosphate uridyl transferase. The major clinical manifestations are vomiting, failure to thrive, and jaundice in early infancy. Tissue toxicity is believed to be due to accumulation of the substrate galactose-1-phosphate. Survivors develop cataracts, cirrhosis, and mental retardation. Therapy consists of removing galactose and lactose from the diet. Substitutes for mammalian milk are used. Those made from protein hydrolysates or those with meat as the protein base are prepared with added vegetable oil and sucrose or glucose as carbohydrate sources. Although soya milk is sometimes employed, some nutritionists are concerned because of the galactose-containing stachyose that is present in these preparations (24). Careful dietary selections must be made for the older child.
because of the widespread use of lactose in unexpected areas, e.g., food stabilizers, such as agar and gum arabic in pills as the "inert" base, and in certain foods in which dried milk powders are used. Adult patients appear to be able to tolerate some galactose, but the pregnant mother of probands should be on a restricted regimen and should be encouraged to avoid alcohol, which may further impair galactose utilization. There is speculation that there are at least three forms of galactos-emia that are variable expressions of the same genetic disturbance (25).

**Hereditary Tyrosinemia**

Hereditary tyrosinemia is a relatively "new" disorder but has been the subject of two major conferences (26, 27) and increasing attention in the literature. The liver manifestations are characterized by acute hepatic necrosis in the young infant, chronic nodular cirrhosis in survivors, and malignant hepatomas in some older infants and children. A hemorrhagic diathesis, hypoglycemia, and hypoproteinemia are early complications and renal tubular insufficiency develops with increasing age. Two hypotheses have been suggested to explain this disorder, i.e., a) a deficiency of p-hydroxy-phenyl pyruvic acid (pHPPA) oxidase (28), or b) a primary defect in methionine metabolism (29). Of these speculations, pHPPA oxidase deficiency appears to be the more popular and explains most of the clinical and biochemical features.

Since most of phenylalanine ingested is catabolized via its oxidation to tyrosine, both amino acids must be limited in the patient's diet. Limiting the levels of both phenylalanine and tyrosine to 50-100 mg/kg per day, with supplemental doses of vitamin D (10,000 units or more) results in improved hepatocellular and renal tubular functions, and healing of the rickets. A prepared formula is available for younger infants. Most natural solid foods contain similar quantities of tyrosine and phenylalanine. Owing to the long familiarity with phenylalanine-containing food in the treatment of phenylketonuria, it is advisable to use these estimations as the basis for planning the daily dietary regimen. Knowledge of the long-term problems associated with prolonged use of this amino acid-deficient diet is limited. Prophylactic dietary therapy of newborn siblings of affected patients is indicated if the former have significant tyrosuria and subsequently demonstrate an abnormal tyrosine-loading test.

**Wilson's Disease**

*Hepatolenticular Degeneration*

Wilson's disease is an unusual familial disorder of copper metabolism characterized mainly by chronic liver disease, extrapyramidal central nervous system dysfunction, and renal tubular damage. Unlike the adult variety of the disease, 80% of patients in the pediatric age group show predominantly hepatic manifestations (30). Although Kayser-Fleisher corneal rings and hypoceruloplasminemia are the two most common features of the disease, presence of both findings is not absolutely necessary for the diagnosis. The Kayser-Fleisher rings may be demonstrable only with a slit-lamp examination, and up to 5% of proven Wilson's disease may have a normal level of serum ceruloplasmin at some time during the course of their illness.

Treatment involves restriction of copper intake to the minimum level compatible with adequate nutrition and growth, i.e., approximately 1 mg daily. The average child's daily diet contains about 4-5 mg copper, the major sources being seafood, nuts, chocolate, and liver. Potassium disulfide has been advocated to chelate copper and to reduce its absorption from the in-

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2 Formula 3200B, Mead Johnson & Co.
testinal tract, but its effectiveness in this regard is disputed and it is very unpalatable. In children, both the hepatic histopathology and clinical problems are often indistinguishable from ordinary post necrotic cirrhosis, and, therefore, outside of the copper restrictions, nutritional management is not unlike the routine approach to other varieties of cirrhosis.

**Hereditary Fructose Intolerance**

This disorder of fructose metabolism begins with the infant's first contact with fructose-containing foods. It is characterized by vomiting, hypoglycemia, failure to thrive, and hepatosplenomegaly, which progresses to cirrhosis in the untreated child. Fructose and sucrose must be strictly avoided and it is not uncommon to find the older patient with an aversion to sweets and fruits.

**The "Fatty Liver"**

Fatty infiltration or fatty metamorphosis is frequently found in autopsy specimens of children dying with a wide variety of diseases. In most of these cases it is unlikely that biochemical or clinical manifestations of hepatic dysfunction were apparent during life. However, widespread, almost massive, steatosis is found in kwashiorkor, Reye's syndrome (31), occasionally in patients with cystic fibrosis (16), and in diabetes and tuberculosis. An adequate intake of protein will usually clear the liver fat in patients with kwashiorkor. In exceptional circumstances, fat-free septal cirrhosis will result in long-standing untreated cases. Reye's syndrome, often following an upper respiratory infection, presents with encephalopathy and hepatomegaly and has a fatality rate of about 30%. Biochemically, hypoglycemia and elevated transaminases are common features, and tissue studies show marked fatty changes of the liver and kidney, and occasionally the pancreas. The etiology is still obscure, and although viral and toxic factors are most often considered, there is no clear evidence to support either hypothesis. Therapeutic measures are mainly symptomatic, and a high carbohydrate diet with adequate protein appears necessary for rapid recovery.

**SUMMARY**

A flexible approach is desirable to provide nutritional requirements for the child with various liver diseases. The needs of the growing child combined with the complexities of hepatic dysfunction preclude rigid rules of management for the child with liver disease. The chronically ill child is manipulative and unpredictable, adding further difficulties to the harassed medical and paramedical personnel interested in his recovery. The apparent disproportionate interest in metabolic disorders is less to stress their frequency than to inform the physician who may not see many children in his practice.

**REFERENCES**

Nutrition and Liver Disease