

ARCHIVES OF DISEASE IN CHILDHOOD

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Annotations

Nutritional support in liver disease

Recent developments in paediatric liver transplantation have highlighted the need for nutritional support in children with chronic liver disease.¹ Malabsorption and a profound metabolic disturbance inevitably leads to protein energy malnutrition.²⁻⁴ Poor nutritional status is an important determinant of survival after liver transplantation and its correction enhances quality of life substantially.⁵

Pathophysiology of malnutrition in liver disease

The mechanisms leading to protein energy malnutrition in liver disease are poorly understood. It is clear that anorexia and fat maldigestion are major problems especially in a child with cholestasis.^{2,4} Steatorrhoea develops when the intraduodenal bile salts fall below the critical micellar concentration necessary for solubilisation of long chain triglyceride and essential fatty acid and fat soluble vitamins deficiencies result.⁶

In adults abnormal gluconeogenesis leads to reduced glycogen stores, hypoglycaemia, and early recruitment of fat as an energy substrate.⁷ Nitrogen metabolism is also disturbed in end stage liver disease with poor clearance of aromatic amino acids.⁴ The peripheral oxidation of protein that occurs secondary to abnormal carbohydrate metabolism may account for the severe muscle wasting often seen in paediatric liver disease.^{3,4}

Portal hypertension is associated with an enteropathy and ascites which may cause feed intolerance and exacerbation of protein energy malnutrition.⁷

The pattern of malnutrition in liver disease

Severe malnutrition (weight and/or height more than 2 SD below the mean) affects 50% of children with established cirrhosis.^{1,8} In children with less advanced liver disease, the mid-arm circumference and mean triceps skinfold measurements are depressed before reduction in weight and height.³ The early reduction in muscle and fat which is characteristic of protein energy malnutrition in liver disease may relate to peripheral oxidation of muscle, fat malabsorption, and preferential recruitment of fat as an energy substrate.^{2,4,7}

The morbidity associated with protein energy malnutrition includes developmental delay particularly locomotor skills,¹ immune impairment,⁹ and infection.⁵

Indications for nutritional support

The need for nutritional support is often underestimated. Infants with liver disease are frequently voracious eaters in the first few months of life. Assessment of growth based on weight alone is confounded by fluid retention and visceromegaly. Stunting may not be apparent until 1 year of age.^{3,4} It is therefore, essential to measure serially height, weight, triceps skinfold, mid-arm circumference, and head circumference. Triceps skinfold and mid-arm circumference measurements are particularly important and a simple calculation can convert the values to give an estimate of mid-arm fat and muscle areas.^{1,3}

Ideally growth failure should be anticipated and prevented, but as a rule of thumb, urgent and aggressive support is indicated if the mid-arm circumference is less than 10 cm after 1 month of age or less than 13 cm from 4 months of age and the triceps skinfold is less than 4 mm after 1 month or less than 5.5 mm from 4 months, that is more than 2 SD below the mean.^{2,3} In older children a deterioration of anthropometric indices may be clear from the history, but again mid-arm circumference and triceps skinfold are the most sensitive indicators of the need for nutritional support, especially if below 10th centile (mid-arm circumference ≤ 14 cm and triceps skinfold ≤ 8 mm ages 1-3 years, ≤ 15 cm and ≤ 9 mm ages 3-6 years, and ≤ 16 cm and ≤ 8 mm ages 7-10 years for boys and girls¹⁰) or obviously dissimilar from height and weight centiles.

Strategies for nutritional support in liver disease

INCREASED ENERGY INTAKE

Resting energy requirements of children with liver disease are increased.¹¹ The metabolic costs of sepsis and fat malabsorption increase energy requirements further. The first step is therefore an increase in energy intake that may range from 140-200% of the recommended daily allowance depending on individual circumstances.^{2,12,13} This is achieved in babies by supplementing feeds with extra fat (up to 8 g/kg/day) and carbohydrate (up to 15-20 g/kg/day) and encouraging older children to consume more fat. Feed supplementation may produce a feed with an energy density of 4.18 kJ (1 kcal)/ml with a high osmolality of 500-800 mosmol/l, so it is important to introduce the additions gradually over several weeks in order to establish intestinal tolerance.

IMPORTANT COMPONENTS OF AN ENTERAL FEED

Many patients will fail to respond to an increase in energy intake alone and will need a more fundamental revision of their diet which often requires delivery by nasogastric tube.

Fat

Medium chain triglyceride (MCT) should be substituted for 50–70% of the long chain triglyceride (LCT). MCT is more soluble and does not need lipolysis and is absorbed even when intraluminal bile concentration is low.⁴ MCT improves growth and steatorrhoea in liver disease.¹⁴ The intake associated with the best growth and satisfactory essential fatty acid status has not been established.

Essential fatty acids

The requirements for linoleic and linolenic acids in children with liver disease are not accurately known. The risk of deficiency is increased by jaundice, protein energy malnutrition, and when intake of essential fatty acids is less than 500 mg/kg/day.⁶ A ratio of linoleic to linolenic acid of 5:1 is recommended because this is close to the ratio observed in breast milk. Excessive intake of linoleic acid may suppress metabolism of linolenic acid to longer chain derivatives.¹⁵

Fat soluble vitamins

Treatment focuses on providing extra oral doses of fat soluble vitamins prescribed separately. Proprietary multi-vitamin preparations are inadequate.² Up to 20 times the recommended daily amount may be needed to produce therapeutic plasma concentrations of vitamins A and E and prevent the occurrence of rickets and a prolonged prothrombin time (for example 5000–20 000 units of vitamin A, 100–800 mg vitamin E, 50–150 µg/kg of alphacalcidol, and 5–10 mg vitamin K daily).⁴

Carbohydrate

The need to restrict fluid intake in some patients with liver disease means that a complex carbohydrate (for example maltodextrin) is useful in order to restrict osmolality in the feed while maintaining a high energy density.

Protein

Up to 4 g/kg/day of protein may be tolerated by children with advanced liver disease without precipitation of encephalopathy.¹¹ Pancreatic function is well preserved even in advanced liver disease.¹⁶ A whole protein source is therefore preferred because of its trophic effect on the gut and improved palatability. The property of branched chain amino acids (BCAA) to undergo extrahepatic metabolism is utilised in feeds that provide additional BCAA.⁴ In adults the results of BCAA supplementation are conflicting, although the one study conducted in children awaiting liver transplantation suggests that BCAA supplementation is associated with improved nutrition.⁸

NASOGASTRIC TUBE FEEDING

Despite a good appetite initially, most infants and children become anorexic after a few months and need nasogastric tube feeding. This approach is highly effective in reversing protein energy malnutrition and may induce a transformation in the child's affect and body habitus such that voluntary oral intake also improves.^{12 13} After 3–5 days' training

in hospital, most parents and older children are able to pass the fine bore Silk tube themselves and program the peristaltic pump. The fear that the passage of a nasogastric tube may increase the risk of variceal haemorrhage is common but groundless.⁸ Long term behavioural problems associated with feeding can be minimised if nasogastric tube feeding is nocturnal, allowing normal oral stimulation during the day. Gastrostomy feeding is avoided because of complications related to ascites and potential problems of access to the abdominal cavity during a liver transplant operation.

COMMERCIALLY AVAILABLE FEEDS

Pregestimil (Bristol-Myers) and Pepti-Junior (Cow and Gate) are frequently used when nutritional support is first required as they provide 40–50% MCT respectively in a nutritionally complete feed which is easily prepared. The hydrolysed protein in these feeds reduces the palatability especially for older children. Portagen (Bristol-Myers), MCT Duocal and MCT Pepdite 2+ (Scientific Hospital Supplies, SHS) can no longer be recommended in liver disease because the high proportion of fat as MCT (83%) leads to essential fatty acid deficiency.⁶

MODULAR FEEDS FOR ADVANCED LIVER DISEASE

Once complications develop (for example ascites, encephalopathy) the use of a modular system where components of a feed are prescribed individually becomes essential as it allows each feed component to be independently varied. For example: Calogen and Liquigen emulsions (SHS) can supply a mix of LCT and MCT, Maxijul LE and Super Soluble Maxipro (SHS) provide carbohydrate and protein components. Generaid (SHS) contains whey protein enriched with BCAA and may be used instead of Maxipro, but it is still being evaluated in children with liver disease.

Occasionally parenteral nutrition is required for a child with end stage liver disease when enteral feeds or infection precipitates protracted diarrhoea. Parenteral nutrition may improve encephalopathy, but is usually regarded as an indication for liver transplantation.

Outcome of nutritional support

Improved growth has been demonstrated in a number of studies in which increasing energy intake,¹² tube feeding,¹³ MCT,¹⁴ and BCAA have been evaluated.⁸ Reduction in mortality after liver transplantation has been associated with better nutritional status.⁵ In children with rapidly deteriorating hepatic function normal growth may be hard to achieve, but prevention of further deterioration is important while waiting for liver transplantation. Effective intervention depends on early recognition and a multi-disciplinary approach. Nutritional support in liver disease remains a challenging area.

S V BEATH
*I W BOOTH
D A KELLY

*The Liver Unit,
Children's Hospital,
Ladywood Middleway,
Birmingham B16 8ET*

**Institute of Child Health,
University of Birmingham,
Nuffield Building, Francis Road,
Birmingham B16 8ET*

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Cytokines in childhood rheumatic diseases

The term cytokines now embodies a large group of important polypeptides whose functions are extremely diverse but are responsible for growth and differentiation of cells, cell to cell signalling, which include mediating the immunological responses and inflammatory responses, and hormonal functions: endocrine, autocrine, and paracrine. The classification of these multifunctional proteins is still evolving. They can be either classified according to their functions, or to their structural similarities.

There are now 12 interleukins which are proteins or polypeptides that mediate cell to cell signalling of the leucocytes. These can be subdivided to the largely monocyte derived cytokines and lymphocyte derived cytokines. This division has some advantage in approximately defining two broad groups of function – that is, inflammatory and immune (see table 1).

Another broad group of cytokines are called growth factors, which are mainly involved in the differentiation and maturation of stem cells into the different lineages in bone marrow (see figure). One can see already some of the overlap, for example interleukin-1 (IL-1) and IL-6 also have differentiation and growth functions as well as being important in cell signalling. A third group of cytokines are the interferons, which have antiviral properties as well as cell regulatory and differentiation properties.

Finally, there is another group of proteins, which are important for matrix formation especially in fibrous tissue, bone, and cartilage – that is, the transforming growth factors and bone morphogenic proteins. This is by no means a comprehensive list but very roughly categorises them according to their main functions.

It is becoming clear that there are complex homeostatic mechanisms within this cytokine network, for example IL-4 and IL-10 and the newly discovered IL-12 reduce synthesis of IL-1 and tumour necrosis factor- α (TNF- α) and could therefore be classified as anti-inflammatory cytokines, although they have other immunoregulatory roles in lymphocyte function. Other so called anti-inflammatory cytokines include transforming growth factor- β_1 (TGF- β_1). The inflammatory cytokines are IL-1, TNF- α , and IL-6. (Their functions are listed in table 2.) All the interleukins have soluble receptors that are thought to be shed from the cells rather than actively secreted. These soluble receptors act as inhibitors of the cytokines and thus modulate their biological activities. There is one exception, the IL-6 receptor acts as an agonist for IL-6, because it can still interact with the signalling protein on the cell membrane (gp130).

In acute inflammation there is activation of effector cells like macrophages by for example bacterial polysaccharides, and inflammatory cytokines are produced. The outcome is dependent on the quantity of the cytokines in the immediate local environment of the cell or tissue. This is determined by the short half life of the cytokine, and by the neutralising effect of its inhibitor(s). Measurement of circulating cytokines in infection and rheumatic diseases (for example rheumatoid arthritis) have shown correlation with disease activity. For example, the TNF- α concentration is high in endotoxin shock, in the cerebrospinal fluid of cerebral malaria, and in the plasma of active rheumatoid arthritis. In the latter case, both IL-1 and IL-6 also parallel the disease activity.¹ A transgenic mouse model of TNF- α over expressed in the joint has shown classic erosive arthritis that mimics rheumatoid arthritis. However, the case for TNF- α being the 'master cytokine' is not proved in rheumatoid arthritis where all three cytokines are always found at the same time. These results emphasise the limited use of measuring circulating cytokines in rheumatic

Table 1 Monocyte and lymphocyte derived cytokines

Monocyte derived cytokines	Lymphocyte derived cytokines
Interleukin-1 α (IL-1 α)	Interleukin-2 (IL-2)
Interleukin- β (IL-1 β)	Interleukin-3 (IL-3)
Interleukin-6 (IL-6)	Interleukin-4 (IL-4)
Interleukin-8 (IL-8)	Interleukin-5 (IL-5)
Interleukin-11 (IL-11)	Interleukin-9 (IL-9)
Tumour necrosis factor- α (TNF- α)	Interleukin-10 (IL-10)
	Interleukin-12 (IL-12)

Table 2 Comparison of IL-1, TNF- α , and IL-6

Biological property	IL-1	TNF- α	IL-6
Endogenous pyrogen fever	+	+	+
Hepatic acute phase proteins	+	+	+
T and B cell activation	+	+	+
Non-specific resistance to infection	+	+	+
Stem cell activation	+	-	+
Fibroblast proliferation	+	+	-
Slow wave sleep	+	+	-
Cyclo-oxygenase; PLA ₂ gene expression	+	+	-
Synovial cell activation	+	+	-
Endothelial cell activation	+	+	-
Shock syndrome	+	+	-
Induction of IL-1, TNF- α , IL-6, and IL-8	+	+	-
Cell adhesion	+	+	-