Nutritional Management of Cholestatic Syndromes in Childhood

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Key Words

Liver disease • Lipid-soluble vitamins • Vitamin E • Malnutrition • Enteral nutrition • Parenteral nutrition • Liver failure

Abstract

Cholestatic liver disease causes severe risk of malnutrition which includes protein-energy malnutrition and specific nutritional deficiencies. The nutritional status can be assessed based on anthropometric measurements, which can be misleading because of ascitis and peripheral edema. Biochemical determinations of lipid-soluble vitamin status are important to evaluate requirements. Based on nutritional status assessment, nutritional therapy should be planned according to a well-defined schedule. The basic principle of nutritional management is to correct the nutritional status as well as to reduce the risk of nutritional deficiencies. Children with cholestasis usually need extra energy supply that can be obtained by increasing energy density of feeds or addition of glucose polymers and lipids. For catch-up growth, usually, protein intake should be increased. Lipid-soluble vitamin supplementation deserves special attention and it is not easy to correct poor vitamin E status. For some children, parenteral administration of vitamin K is needed. Since recently, a water-soluble vitamin E (d- α -tocopheryl polyethylene glycol 1000 succinate) given by oral route is used with a good therapeutic effect. As the liver disease progresses to liver

failure in many chronic cholestatic diseases, nutritional therapy can often be regarded as 'bridging' for liver transplantation to improve prognosis. Thus, invasive nutritional support is justified in severe liver disease which usually includes nocturnal nasogastric tube feeding, or even parenteral nutrition.

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Introduction

Requirements of specific nutrients for healthy infants and children are widely discussed and recommendations are updated every few years. There are still many controversies concerning some nutrients. Recently, vitamin K supplementation in infancy was a matter of debate. Ijland et al. [1] questioned the safety of oral vitamin K supplementation in a daily dose of 25 μ g in a healthy population as bleeding occurred in 6 breastfed infants in the population studied. Apparently, 5 out of 6 bleeding infants were cholestatic children with biliary atresia. Thus, cholestasis caused the risk of vitamin K deficiency and the results do not necessarily point to the need to change recommendations for healthy infants. One should be aware that these recommendations do not apply to cholestasis which is a specific risk group. Cholestatic liver disease should be recognized early and specific treatment started as early as possible. Many cholestatic liver diseases progress to

liver insufficiency and require liver transplantation. Nutritional therapy seems to be one of the priorities and can be regarded as a 'bridging' for liver transplantation. Nutritional status is an important prognostic factor, and children with better nutritional status have fewer complications and lower mortality at liver transplantation [2]. This is the reason why we recently elaborated and published guidelines on nutrition of infants with cholestatic liver disease [3].

We have almost forgotten diseases related to specific nutrient deficits. Recently, Samonte et al. [4] described a young girl who underwent liver transplantation and had a long battle with complications presenting as end-stage renal disease and liver failure. She developed classical oral signs of scurvy which were confused with cyclosporine toxicity, skin changes suggested vasculitis and bone aches were regarded to be related to renal osteodystrophy or corticosteroid-induced osteoporosis. Finally, it appeared that the disease was caused by vitamin C deficiency. In the editorial to this publication, we indicate that there are still situations where we can find basic diseases, caused by deficiency of one nutritional component [5]. Severe liver disease with cholestasis is a very good example of these nutritional problems.

In this chapter, causes of malnutrition, specific nutrient requirements and a nutritional approach to children with cholestatic liver disease are presented and discussed.

Causes of Malnutrition

Diminished bile flow leading to decreased intraluminal bile acid concentration seems to be the major pathomechanism responsible for malnutrition. Cholestasis leads to a significant decrease in lipid absorption and long-chain triglycerides require bile acids for utilization. Lipids significantly contribute to energy uptake, and thus, their malabsorption may cause a negative energy balance. High requirements of other nutrients like protein and carbohydrate are also documented. Many studies show that absorption and utilization of lipids and lipid-soluble vitamins is a process of several stages: dispersion in lipid emulsion, solubilization into mixed bile salt micelles, movement across the unstirred water layer adjacent to the microvilli, cellular uptake by intestinal mucosal cells, incorporation into chylomicrons, and secretion into the lymph. Absorption of some vitamins in cholestasis may be severely reduced, like vitamin E or β -carotene; other vitamins are better utilized, and high-

dose supplementation can efficiently balance poor absorption. There are several other indicators of deficiency risk that should be evaluated: low caloric intake, unbalanced diet with low fat and vegetable consumption, increased oxidative status due to recurrent infections and some other chronic disease conditions complicating liver disease. For these high-risk groups, special attention is needed.

Increased energy expenditure was also documented in cholestasis and it can increase up to 40% or more for body weight in malnutrition but it is normal if calculated for age [6, 7]. Anorexia is a common problem of advanced liver disease and it can be attributed to organomegaly or ascitis. Portal hypertension with naturally occurring shunts may have central effects of unidentified toxins. As important growth hormones like insulin-like growth factor 1 and its binding proteins are produced by the liver in response to circulating growth hormone, cholestasis and portal hypertension may lead to abnormal insulin-like growth factor 1 axis response. These abnormalities cannot be corrected by hyperalimentation [8].

Can We Use a Standard Approach to All Cholestatic Diseases?

In general, severe cholestasis progressing to end-stage liver disease causes significant malabsorption and requires intensive nutritional management. Still, it is difficult to describe a standard approach. Usually, listing for liver transplantation is an indication for nutritional therapy according to standardized protocols. However, some cholestatic diseases progress slowly to liver insufficiency or may not require liver transplantation. Progressive familial intrahepatic cholestasis (PFIC) can be treated by a surgical procedure described as partial biliary diversion. This treatment is able to stop progression of liver damage, but vitamin or β -carotene malabsorption is not corrected. This disease requires special nutritional attention as vitamin E levels are extremely low in these patients and they are not directly related to the degree of cholestasis. In this disease, severe steatorrhea is often documented, which is not related to pancreatic insufficiency [9]. High requirements of vitamin E supplements are also observed in children operated for biliary atresia, but they correspond well with the degree of cholestasis.

Another metabolic problem discussed in cholestasis is a high cholesterol level observed in Alagille syndrome. Some liver centers use only low cholesterol diet to treat this abnormality, other centers use pharmacotherapy to

lower cholesterol levels. The recent publication comparing intima media thickness as an indicator of atherogenesis in patients with PFIC (presenting with low cholesterol levels) and Alagille syndrome shows that patients with PFIC are at higher risk for cardiovascular disorders involving atherosclerosis. Intima media thickness and wall stiffness were increased in patients with PFIC but not in patients with Alagille syndrome. Total cholesterol, low-density lipid cholesterol, high-density lipid cholesterol and lipoprotein X were remarkably increased in patients with Alagille syndrome, whereas in patients with PFIC, an increase in triglyceride and a decrease in high-density lipid cholesterol were the prominent findings [10]. Thus, a nutritional approach should not primarily aim at decreasing cholesterol levels in Alagille syndrome.

Assessment of the nutritional status may also cause some problems. Short stature is a typical feature of PFIC and it cannot be corrected by nutritional support. That is why height is not a good indicator of nutritional status in PFIC (fig. 1).

Diagnosis of Nutritional Deficiencies

Protein-energy malnutrition can be easily recognized if special nutritional support is not introduced from the early beginning of cholestasis. Children may present with thin limbs and a prominent abdomen. Body weight is not regarded as a good indicator of nutritional status as it is affected by fluid balance abnormalities [11, 12]. However, if ascitis is efficiently managed with diuretics, changes of body weight may be used for the evaluation of nutritional status. Other anthropometric parameters may be used to assess the nutritional status like mid upper arm circumference and triceps skin fold thickness. Height may be affected if malnutrition is prolonged. That is why the assessment of nutritional status may be complicated, and it should also take into account the specific liver disease.

Specific nutrient deficits cannot be easily recognized and they should be prevented as early as possible. However, the clinical symptoms of nutrient deficiencies still occur in clinical practice – scurvy or bleeding are only examples. That is why it is extremely important to detect any signs of malnutrition very early. As pointed out in the guidelines, all children with cholestatic liver disease should have a full nutritional review with an intervention and follow-up plan documented in their case records [3]. Energy, protein, carbohydrate and lipid intake

Fig. 1. Short stature – a 14-year-old girl with PFIC.

as well as vitamin supplements should be recorded. Dieticians must be involved in nutrition assessment and planning. Still, careful dietary monitoring may not be sufficient to avoid malnutrition and significant body composition changes. Some deficiencies may not accompany protein-energy malnutrition and can be precociously detected only by biochemical measurements. This raises the following questions: should lipid-soluble vitamins be evaluated in high-risk group patients? Secondly, should we routinely supplement vitamins and increase energy intake in these high-risk patients? The answer to the first question is positive. We can precisely describe high-risk groups where periodic vitamin evaluation could be beneficial in terms of early diagnosis of deficiency. The answer to the second question is more difficult. Although vitamin K and E supplementation is regarded as safe, excess of vitamins A and D in some circumstances may be detrimental and may cause severe complications.

Jaundiced patients develop osteoporosis more frequently than nonjaundiced patients. Vitamin D defi-

Table 1. Deficiency monitoring – vitamins and minerals

Nutritional element	Clinical signs of deficiency	Signs of toxicity	Biochemical monitoring
Vitamin A	usually not observed – dry skin, xerophthalmia and night blindness	liver fibrosis, hypercalcemia, pseudotumor cerebri and painful bone lesions	serum retinol/RBP ≥ 0.8 serum retinol 250–800 ng/ml
Vitamin D	osteopenia, bone fractures, hypocalcemia, metaphyseal changes, hypophosphatemia, muscle hypotonia and rickets	hypercalcemia and pseudotumor cerebri	25-OH-D serum levels >25 ng/ml
Vitamin E	neuropathy, edema, anemia, skin lesions	not documented in cholestatic children; extremely high doses may affect neutrophil chemotaxis and protein carboxylation vitamin K dependent; safety of supplementation questioned in adults in respect of cardiovascular disease	vitamin E/total lipids ≥ 0.6 mg/g serum α -tocopherol 3.8–16 mg/l
Vitamin K	hemorrhage	not documented	prothrombin time PIVKA II <3 ng/ml
Water-soluble vitamins	usually do not occur; anemia may be related to folic acid and vitamin B ₆ deficiency, neuropathy to B ₁ and B ₁₂ deficiency, and scurvy to vitamin C deficiency	not observed with normal doses	usually not performed; in specific high-risk groups, vitamin C can be monitored
Iron	anemia, behavioral changes	serum ferritin, iron and hemoglobin are not very reliable	
Minerals: calcium selenium zinc phosphate	osteoporosis, osteopenia, bone fractures, growth failure, skin lesions, anorexia, neutropenia	not observed with normal doses; still, selenium given in high doses can be toxic	serum calcium concentration and urinary calcium/creatinine excretion as lab routines, serum selenium, zinc concentration in selected labs
RBP = Retinol-binding protein.			

ciency seems to be responsible. Bone-mineral deficiency can be detected earlier by means of bone mineral density measurement (noninvasive method) than by measuring serum Ca, P and Mg levels in these patients (table 1) [13].

Energy and Carbohydrate Intake

As energy requirements increase significantly in chronic cholestasis, energy-dense feeds can be used to increase caloric intake. In clinical practice, some liver units use concentrated infant formulae for cholestatic infants where energy density may increase up to 50%. Carbohydrates and proteins may be added to normal feeds. Car-

bohydrate is the major source of dietary energy contributing about two thirds of the non-protein energy. Short-chain polymers are currently used in nutritional support as their osmotic load is not high enough to cause diarrhea. Starch may also be used but it can cause bloating and diarrhea if not digested in the small intestine. The patients should be monitored for side effects when short-chain polymers are increased subsequently during a few days. If there are significant symptoms of intolerance, the carbohydrate dose should not be further increased. Even if carbohydrates are used as the main source of energy, lipids can also contribute to the higher energy requirements. Still, carbohydrates are usually better accepted by the patients as they have better taste than lipids or protein.

Calculation of carbohydrates added to the usual feeds should be based on estimated energy requirements, which increase significantly in end-stage liver disease and in biliary atresia with severe cholestasis.

Water and Electrolytes

Fluid requirement is normal for actual weight if restriction is not needed because of ascitis or edema. Sodium should not be supplemented in high amounts to correct hyponatremia as it can cause fluid retention. In infancy, sodium intake of 1 mmol/kg/day and normal potassium of about 2 mmol/kg/day are usually appropriate [3]. It is difficult to find the appropriate balance between fluid restriction and high-energy demand. That is the reason why energy-dense feeds should be used.

Protein

Children with normal growth and weight usually require normal protein intake. Maintenance needs do not appear to be very different from those of healthy children. However, advanced cholestatic liver disease with malnutrition should be managed with intensive nutritional therapy and a higher protein intake to support high rates of catch-up growth. A 10% protein/energy ratio used to rehabilitate malnourished children is generally sufficient to ensure rapid catch-up growth if only energy needs are covered [14]. The specific needs in cholestasis are not clearly described. Infants with severe cholestatic liver disease seem to require a protein intake of around 2–3 g/kg/day. The requirements are lower in cholestasis in childhood as it is the case for healthy children and infants. Infections often observed in biliary atresia (like cholangitis episodes) may further increase energy and protein requirements. In children, proteolysis increases markedly during infections and a negative protein balance may occur [15]. Protein restriction can be considered only if encephalopathy is present – that is in case of liver failure and of portosystemic shunts related to portal hypertension. Hyperammonemia does not justify protein restriction, in absence of encephalopathy.

A polymeric diet is systematically used for infants and children with cholestatic liver disease. Protein hydrolysates may be considered in enteral nutrition or temporarily in severe malnutrition. The taste of feeds should also be considered as an important factor as poor palatability

may further decrease energy intake. Thus, hydrolysates can be used only in very specific clinical situations.

Recently, branched-chain amino acids were tested in animal models and in clinical settings of biliary atresia [16, 17]. They improved weight gain, muscle mass, nitrogen balance and also led to increased total body potassium, mid upper arm circumference and subscapular skin-fold thickness in cholestatic children.

The recent guidelines proposed an ideal product which would include protein as 3 g/kg/day of whey proteins, being approximately 2.6 g/100 ml reconstituted formula, enriched in branched-chain amino acid to 10%, treating hyperammonemia instead of reducing protein intake [3].

Lipids

The dietary supply and metabolism of lipids in early childhood are of major importance for growth, body composition and child development. The choices of dietary lipid during the first years of life are of great practical importance for growth and development not only in healthy infants and children, but even more in children with hepatic disorders. Lipids are the major source of energy supplied by human milk. The supply of dietary lipids is also important for providing essential lipid-soluble vitamins and polyunsaturated fatty acids (PUFAs) [18].

Lipids as Energy Source

Lipid absorption is markedly decreased in cholestasis which leads to decreased energy intake. Thus, it is important to balance the energy losses with extra energy supply. Carbohydrates may increase energy density of feeds to some extent but they are not sufficient to cover all energy needs. Lipids are less palatable, but other features of this macronutrient make it a valuable dietary supplement: high energy density, low osmolarity and content of essential PUFAs. Steatorrhea may limit lipid use in nutritional support, even though in a child with steatorrhea, growth may improve if lipids, given in higher amounts, increase fat intake [19]. Medium-chain triglycerides (MCTs) can be optionally used as a lipid supplement or as an MCT-enriched formula. MCTs do not provide the same energy balance as long-chain triglycerides (LCTs) but they are successfully used in the treatment of fat malabsorption because they have a high water solubility and are rapidly cleaved by lipases [20]. However, because of the shorter chain length of their fatty acids, their energy content (per gram of fat) is about 16% lower than that of LCTs. MCTs

are rapidly oxidized and have a high thermogenic effect. They reach the liver directly via the portal flow without need for formation of mixed micelles but they are also ketogenic [21]. Larger amounts of dietary MCTs are metabolized in several tissues by carnitine-dependent mechanism and may increase the need for carnitine [22]. One may estimate the proportion of 30–50% of total lipids as MCTs as the optimal for nutritional management in cholestasis [23, 24]. Still, it is difficult to specify the ideal dietary fat content and ratio of MCTs to LCTs. Limited data point to better fat solubilization and growth of cholestatic infants fed with 30 or 70% MCTs against a 50/50% mixture of MCTs/LCTs [25]. Essential fatty acid deficiency was described with the use of very high MCT content in the diet which was not sufficiently supplemented with PUFAs [23]. Most of the infant formulae with MCTs have an MCT/LCT ratio of about 1/1 and are supplemented with essential fatty acids. The MCT-rich formulae for children may contain higher amounts of MCTs (75 to >80% of lipids; e.g., Caprilon and Portagen) even though they are supplemented with essential fatty acids. Special attention is needed if pure MCT oil is used as a dietary supplement, and in this situation, a detailed dietary assessment is required. PUFA-rich vegetable oils should also be used to support adequate intake of essential fatty acids. Lipid intake and MCT ratio should be titrated against optimal weight gain and growth and intolerance of nutrients. Lipids should be used to increase energy density and a proportion at least similar to that for healthy age-matched children (from 30 to 50%) seems to be reasonable [3].

Polyunsaturated Fatty Acids

Long-chain PUFAs (LCPs, PUFAs with a carbon chain length >18), such as arachidonic (AA) and docosahexaenoic acid (DHA), are important for early human growth and development of membrane-rich tissues such as the brain and retina [26]. PUFAs are also precursors of eicosanoids with important biological roles as mediators of immune and vascular functions and platelet aggregation, making PUFA deficiency (especially from the n-6 series) a concern. The classical essential fatty acids linoleic acid (18:2n-6) and α -linolenic acid (18:3n-3) must be delivered with the diet and then are elongated in the liver and in the brain to obtain LCPs [18]. Breastfed infants receive appreciable amounts of preformed AA and DHA with human milk lipids [27]. In contrast to infants fed with human milk, those fed conventional milk formulae based on vegetable oils do not receive appreciable amounts of LCPs with their diet and depend on the utilization of

body stores or endogenous synthesis from essential fatty acid precursors for LCP provision for growing tissues. Koletzko et al. [28] estimated conversion rates of linoleic acid with a stable isotope technique and found that the contribution of AA synthesis to the total plasma AA pool is only about 6% per day. Still, to draw any conclusions on the benefits of LCP supply in infancy, strong evidence from randomized clinical trials is needed. A Cochrane review of 2004 reviewed publications on LCP supplementation in term infants up to 2001 which included studies on visual acuity as well as on cognitive function and psychomotor development [29]. Different methods were applied to measure the functional effects of supplements which causes difficulties for drawing conclusions. The authors concluded that a beneficial effect of LCP supply on information processing is possible, but larger studies over longer periods are suggested to further investigate this issue. In a critical review of the available publications, Uauy et al. [30] pointed out that some studies that did not find advantages of LCPs either used low concentrations of DHA or did not include an assessment of compliance.

Recent publications which were not included in the Cochrane review studied later LCP supply in infants after weaning from breastfeeding in the first months of life. Birch et al. [31] studied infants who were weaned after about 6 weeks of human milk feeding to formula without or with LCPs and found poorer visual acuity at 17, 26 and 52 weeks of age in the infants who received no LCPs. Similarly, Hoffman et al. [32] observed faster maturation of evoked visual potentials at 1 year of age in infants supplemented from 4 months of age. Moreover, recently, it was demonstrated that early LCP supplementation may influence both the presence of specific immune cell types and function [33].

As estimation of PUFA and LCP requirements is not easy for healthy infants and children, it is even more difficult to give recommendations for children with cholestasis. Still, one should be aware of the risk of PUFA deficiency, and some case reports appeared describing classical dermatological symptoms of essential fatty acid deficiency [34]. There are several factors that contribute to PUFA and LCP deficiency including low PUFA intake, malabsorption and disturbed metabolism of PUFAs to long-chain derivatives. We reported LCP and PUFA deficiency as expressed by plasma phospholipid levels in spite of adequate PUFA content in the diet of cholestatic infants [35]. Extra PUFA intake may improve fatty acid status (e.g., soybean or rapeseed oil) and, in infancy, it seems it should significantly exceed 10% of total energy.

Supplementation of essential fatty acids may not be sufficient. We were able to show increasing impairment of hepatic PUFA conversion to LCPs with an advancing severity of liver disease; thus, severe cholestasis is a significant risk factor for LCP deficiency even with essential fatty acid supply [36]. LCP supplementation can be required based on dietary products like egg yolk (rich in AA) or fish oil (rich in DHA). Infants may be given conventional LCP-supplemented formulae available for healthy term and preterm infants or dietary supplements. Not only low intake, impaired metabolism and decreased absorption may play a role in PUFA deficiency. Unsaturated fatty acids may undergo lipid peroxidation, and increased lipid peroxidation is observed in cholestasis due to impaired antioxidant defense. Even if we observed high lipid peroxide levels and low vitamin E concentrations we were not able to show any direct relationship between PUFAs and lipid peroxides [37, 38]. Profound LCP deficiency may develop in advanced cholestatic liver disease and it can be difficult to correct. It was documented that even 1 year after liver transplantation, the LCP status is not entirely reversed [39]. At the moment, there are no studies showing functional effects of LCP supplementation in children with cholestasis and we cannot give strong recommendations on PUFA and LCP supplementation. It is reasonable in clinical practice to use PUFA-rich vegetable oils and/or egg yolk as dietary supplements to increase energy density and PUFA intake. In infants with cholestasis who receive regular infant formulae and do not require MCT-enriched feeds, LCP-supplemented infant formulae may be used [3].

Vitamins

Lipid-soluble vitamin malabsorption seems to be the major nutritional problem and very specific to cholestasis. Some other factors may also contribute to low lipid-soluble vitamin levels like utilization of vitamin E due to increased free radical formation. Some lipid-soluble vitamins can be efficiently supplemented (vitamins A, D and K), while vitamin E supplementation may cause significant problems. In severe cholestatic liver disease, the oral route of vitamin supplementation may not be sufficient, and parenteral formulations should be considered.

Vitamin A Deficiency

Vitamin A deficiency presents with dry skin, xerophthalmia and night blindness. Serum levels are often used to estimate vitamin A status but they do not correctly re-

flect vitamin A status. A useful indicator of vitamin A status is the plasma retinol/retinol-binding protein molar ratio [calculated as serum retinol (ng/dl)/serum retinol-binding protein (mg/dl) $\times$ 0.0734]. Ratios exceeding 0.8 point to normal vitamin A status. Vitamin A liver metabolism is usually preserved in cholestatic patients [40, 41]. Higher ratios can be associated with toxicity including liver fibrosis, hypercalcemia, pseudotumor cerebri and painful bone lesions. Vitamin A toxicity can be well documented from plasma levels of vitamin A esters. As vitamin A can be toxic, one may consider β -carotene supplementation as a precursor of vitamin A. It is also a lipid-soluble substance that is involved in the protection of membranes against free radical injury complementary to vitamin E and it can be safely used as a supplement in patients with liver disease, contrary to vitamin A supplementation. There is good evidence from in vitro studies that β -carotene is a potent antioxidant that may alleviate the toxic effect of bile acids on liver cells [42]. Also, β -carotene deficiency was reported in adults with prolonged cholestasis [43]. We recently reported low β -carotene levels in children with cholestasis that may be related to poor absorption of this substance from the gut (data ready for publication).

Vitamin D Deficiency

Vitamin D deficiency may also easily develop in prolonged cholestasis. Breastfed infants are at a higher risk, as breast milk contains low amounts of vitamin D. Symptoms of profound vitamin D deficiency can be rarely observed – like hypocalcemia, hypophosphatemia, muscle hypotonia and rickets. In severe liver disease, it is not only poor vitamin D absorption which is responsible for poor availability of vitamin D but also impaired metabolism in the liver can play a significant role. This is why vitamin D is not used to correct a deficiency but instead its metabolite 25-hydroxycholecalciferol (25-OH-D). One should be aware that vitamin D supplementation alone is not effective, and calcium and phosphorus should be given simultaneously. However, treatment with vitamin D does not always prove successful in improving the bone disturbance [44]. Sunlight exposure can be of some help but it is not sufficient. The best indicator of vitamin D status in cholestasis is 25-OH-D serum concentration; levels of 20 ng/ml and less are regarded as extremely low, and the optimal values in healthy subjects are discussed. Concentrations significantly exceeding 25 ng/ml can be regarded desirable. The simple indicator of hypocalcemia can also be used – the urinary calcium/creatinine ratio should be <0.25 . However, there is no direct correlation

between severity of osteopenia and serum levels of 25(OH)-vitamin D and 1,25(OH)₂-vitamin D in either infants or older children with cholestasis. Decreased bone mineralization in childhood cholestasis is a disease process that begins early in infancy, rapidly worsens with increasing age and hepatic dysfunction, and remains relatively stable in children with more stable liver disease [44]. Vitamin D toxicity is seldom reported and includes hypercalcemia and pseudotumor cerebri. Liver transplantation seems to correct osteopenia and vitamin D deficiency. In infants and children younger than 2 years with chronic cholestasis, the bone mineral content normalizes approximately 11 months after orthotopic liver transplantation. This normalization was preceded by a sustained period of normal serum 25-OH-D levels [45].

Vitamin E Deficiency

Vitamin E deficiency seems to be a major problem in prolonged cholestasis which is difficult to correct in some cholestatic diseases. Marked vitamin E deficiency in children with chronic cholestasis leads to neurological degeneration. The most important role of vitamin E is its antioxidative function as an oxygen-free radical scavenger. Insufficient availability of this vitamin may predispose to peroxidation, including that of unsaturated fatty acids, which disrupts the function of central and peripheral nervous system cell membranes. The consequences of vitamin E avitaminosis are particularly serious in children. The initially subtle neurological changes may, after some years, lead to irreversible damage. The neurological signs related to vitamin E deficiency usually include peripheral neuropathy, ophthalmoplegia, ataxia, impaired vibratory sensation and degenerative lesions of the retina. The first signs in the form of disappearance of deep tendon reflexes can manifest themselves relatively early. The nervous system lesions are similar to those observed in other diseases with vitamin E deficiency, such as abetalipoproteinemia, Anderson's disease and familial, selective isolated vitamin E deficiency [46–48].

In many children with cholestasis, it is not possible to obtain improvement in vitamin E status with oral, fat-soluble preparations, which makes it necessary to resort to painful intramuscular injections. Sokol et al. [49–51] reported on the beneficial effect of a new, water-soluble oral vitamin E preparation that corrects α -tocopheryl serum levels and improves existing neurological defects in children with cholestasis. TPGS (d- α -tocopheryl polyethylene glycol 1000 succinate, Eastman Chemical Products Inc., Kingsport, Tenn., USA, or Orphan Europe, Paris, France) is a water-soluble succinic acid ester of vi-

tamin E bound to polyethylene glycol 1000, which can form micelles without the involvement of bile acids. We also reported on the effects of TPGS therapy which quickly normalized serum vitamin E levels but did not improve the increased lipid peroxidation and poor PUFA status [37]. Coadministration of other fat-soluble vitamins in patients with cholestasis can be concerned [52]. Vitamin E therapy monitoring relies on the vitamin E/total lipid ratio (normal >0.8 mg/g but with plasma vitamin E <30 μ g/ml). Toxicity is unusual.

Vitamin K Deficiency

Vitamin K deficiency may be an early sign of fat malabsorption in cholestasis [1] resulting in hemorrhagic disease. Important conclusions came from Dutch and Danish national biliary atresia registries. A daily dose of 25 μ g of vitamin K failed to prevent bleedings in apparently healthy infants with unrecognized cholestasis because of biliary atresia. One milligram of weekly oral prophylaxis offered significantly higher protection to these infants and was of similar efficacy as 2 mg of intramuscular prophylaxis at birth [53]. In clinical practice, high-dose oral vitamin K every week or every 3 days is used for prevention of bleeding. For treatment of a significant prothrombin time, increased intravenous vitamin K management is the best option. Konakion MM (Roche) seems to be a formulation (vitamin K compound solubilized in glycocholate and lecithin) which efficiently and safely corrects vitamin K deficiency [54].

Vitamin K deficiency can be detected by high international normalized ratio values (increased prothrombin time) which is corrected by parenteral vitamin K administration. PIVKA II (protein induced in the absence of vitamin K), measured by ELISA assay, seems to be a better indicator than prothrombin time (PIVKA II >3 ng/ml reflects vitamin K deficiency) but it is not commonly available.

Water-soluble vitamins should also be supplemented as malabsorption of nutrients may also cause water-soluble vitamin deficiency. Moreover, antioxidants may decrease as they are utilized in protection against high peroxide formation. Single nutrient deficiency, like vitamin C, can be even more profound if combined with low levels of other antioxidants (e.g., vitamin E). In chronic cholestasis, it is advised to use twice the recommended dietary allowance for water-soluble vitamins [3], but in some circumstances, much higher doses of particular vitamins are needed [4]. Low levels of minerals and trace elements were documented in children with cholestasis. Supplements of selenium, zinc, calcium and magnesium

Table 2. Lipid-soluble vitamins in the management of cholestatic children

Lipid-soluble vitamin	Daily requirement	Method of administration
Vitamin A	<10 kg: 5,000 IU >10 kg: 10,000 IU IM: 50,000 IU	oral
Vitamin D	25-OH-D: 2–5 µg/kg IM: 30,000 IU, 1–3 monthly	oral/IM
Vitamin E	TPGS 25 IU/kg IM: 10 mg/kg (max. 200 mg) every 3 weeks	oral
Vitamin K	2 mg/day weekly 5–10 kg: 5 mg >10 kg: 10 mg IM: 5–10 mg every 2 weeks	oral IM

According to Baker et al. [3]. IM = Intramuscular; max. = maximum.

should be given as guided by plasma levels [3]. Selenium and zinc are important antioxidants. Iron may enhance oxidative stress and fibrogenesis in patients with liver disease [55]. Thus, iron should not be supplemented on a regular basis. Iron deficiency does not seem to be a common problem in cholestasis. Liver transplantation seems to correct most of the deficiencies and antioxidant status and restores such capacities except for glutathione (table 2) [56].

Oral, Enteral and Parenteral Route of Administration

The oral route is preferable only if sufficient energy and nutrient supply can be secured. Commercial preparations should be used for oral feeding and a well-balanced diet should be obtained under control of a dietitian. The feeds should be palatable. Energy-dense preparations can be used to increase energy intake.

In advanced liver disease, especially if a fast catch-up growth is required before liver transplantation, nasogastric tube feeding can be the best option. Bolus feeding cannot always be tolerated. Continuous infusion rate obtained by a pump for up to 20 h a day can solve many problems occurring with tube feeding, like vomiting. Night-time nasogastric tube feeding is another option: the child is allowed to eat ad libitum during the day and

Fig. 2. Feeding algorithm for children with cholestatic liver disease.

receives extra energy when sleeping. The daily preparation of the solutions requires involvement of dietitians. The risk of bacterial contamination of feeds should be a concern. Percutaneous endoscopic gastrostomy is not a common way of nutrient supply because of risk of variceal bleeding.

Parenteral nutrition is needed in a very small percentage of patients as usually the absorptive function of the gastrointestinal tract is preserved. Vomiting, bloating, diarrhea and other complications may cause severe problems in oral and enteral feeding. If energy intake is too low for the requirements, partial parenteral nutrition may improve the nutritional status. Still, the safety of this method of nutritional therapy is strongly related to the experience of the clinical center. The standards of parenteral nutrition in cholestasis are similar as for other indications.

Standard amino acid solutions are used, and no benefit of branched-chain amino acids was documented [57]. Also, lipids are well tolerated. We assessed safety of LCT and MCT/LCT lipid infusions in short-term parenteral nutrition in cholestatic children and we found a good metabolic tolerance of both intravenously infused emulsions in infants with cholestasis. As DHA seems to play a major role in brain development, LCT emulsions may be the optimal source of PUFAs (they contain more PUFAs than MCT/LCT emulsions) for infants with chronic cho-

lestasis if given short term. Our results do not show any risk of increased lipid peroxidation with lipid infusions. Plasma lipid concentrations were not changed by either of the lipid emulsions used [58].

Guimber et al. [59] also reported on safety of parenteral nutrition given to cholestatic children. He observed an increase in Z scores for weight for age and weight for height with no significant change in parameters of liver synthetic function in 7 children with liver disease. The significant increase in bilirubin was probably related to the natural course of the liver disease or could be partially explained by parenteral nutrition. Even if prolonged parenteral nutrition is a risk factor of cholestasis in patients who do not present primary liver disease, this method of nutritional therapy can be used as a 'bridging' for liver transplantation.

Conclusions

Cholestatic liver disease deserves special attention concerning nutrition and nutritional support. Nutritional status should be assessed, and specific nutritional needs should be defined before nutritional therapy can be started. The basic principle of the nutritional management is to correct the nutritional status with additional supply of energy proteins, carbohydrates, lipids and lipid-soluble vitamins. As liver disease progresses to liver failure in many chronic cholestatic diseases, nutritional therapy can be often regarded as 'bridging' for liver transplantation to improve prognosis. Thus, invasive nutritional support is justified in severe liver disease which usually includes nocturnal nasogastric tube feeding or even parenteral nutrition (fig. 2).

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