

ETIOPATHOGENESIS AND TREATMENT OPTIONS IN SHORT BOWEL SYNDROME ASSOCIATED WITH CHRONIC LIVER DISEASE

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Abstract

Short bowel syndrome is a life threatening disease with a high mortality and morbidity. Since home parenteral nutrition (PN) has been established, there is an increasing number of patients surviving the acute loss of bowel function. But in the long-time these patients suffer from different complications of PN, with loss of central venous access, recurrent sepsis and finally the syndrome of progressive cholestatic liver disease. Both loss of central venous access and especially the progressive cholestatic liver disease are the limiting factor for the long-term survival of patients suffering from intestinal failure. Interestingly, the pathophysiologic mechanisms of parenteral nutrition induced intrahepatic cholestasis have not been solved yet and seem to be of multifactorial genesis. Cholestasis has shown to be associated with prematurity, recurrent sepsis, enteral and parenteral nutrition, especially with lipid emulsions. Enteral feeding and a well-controlled regime of parenteral nutrition lower the incidence of end-stage liver disease and, therefore, has to be optimized in the therapy of these patients.

Key words: Short bowel syndrome (SBS), parenteral nutrition (PN), liver diseases, intrahepatic cholestasis

Introduction

Short bowel syndrome (SBS) is a result of anatomic or functional loss of major parts of the small bowel, leading to intestinal failure. The estimated incidence for SBS is 24.5 (12.1-36.9) per 100000 live births, with much higher incidence in preterm babies born before 37 weeks of gestation compared with term newborns (1). A cohort study by Wales et al. showed a high mortality of SBS (6-45%)(2). On home parenteral nutrition (PN) survival rates at one and five year have been reported to be 91- 97% and 62-68% in adults and 97% and 89% in children (2).

SBS patients initially require PN and are included in an intestinal rehabilitation program, that optimises the function of the remaining bowel using medical and nutritional strategies(3,4,5).

Nevertheless, in some patients, intestinal autonomy cannot be restored and PN has to be performed for a long period of time(6).

Beside the problems with the central venous access and recurrent infections of the central venous line, the major unresolved problem remains the development of intestinal

failure associated cholestasis and end-stage liver disease(7). Intestinal failure is defined as the inability of the alimentary tract to digest and absorb sufficient nutrients to maintain normal fluid balance, growth and health. Long time parenteral nutrition causes loss of venous access and recurrent catheter infections, however, the major unresolved problems of PN remains the PN associated liver disease.

After Beath et al.(8) the PN associated liver damage can be classified in three stages: early, established and late intestinal failure associated liver disease.

In an early stage there is a persistent elevation of liver enzymes, that are 1.5 times higher than normal, which persist over six weeks in infants and children. Bilirubin is <3 g/L. Liver biopsy shows steatosis in 25% of the liver parenchyma and 50% of the portal tracts show fibrotic alteration. Established liver disease is characterized by elevated liver enzymes, that are more than 1.5 times higher than normal. Bilirubin is between 3 and 6 g/L and liver biopsy shows steatosis in more than 25% of liver parenchyma and fibrosis affecting more than 50% of portal tracts.

The late liver disease is characterized by elevated liver enzymes that are more than three times higher than normal. Bilirubin is >6 g/L. The international normalized ratio is >1,5 and additional signs for portal hypertension may be present. Liver biopsy shows fatty change with areas of intense fibrosis.

The liver damage in PN associated liver damage shows some distinct features that are different from classical liver cirrhosis. Unlike in adults, the most common histologic finding in children is intrahepatic cholestasis rather than steatosis hepatitis. There is an age related histologic alteration. This may reflect the immaturity of the biliary excretion system in neonates and is related to prematurity and duration of parenteral nutrition. Compared to cholestasis in adults, in neonates it occurs early and there is a high incidence of developing progressive cholestatic liver disease (17%)(9). Complete and incomplete block of bile secretion is associated with ductular reaction accompanied by periductular fibrosis. This eventually leads to fibrous linkage of adjacent portal tracts. This stage of "biliary fibrosis" is a potentially reversible lesion(10). Biliary cirrhosis in parenteral nutrition associated liver disease is unusual, but it is the final stage characterized by portal-central fibrous septa and nodular parenchymal regeneration.

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Liver fibrosis is classified according to the criteria of Desmet et al ranging from grade 0-4. Periportal and architectural changes form the base for grading in chronic cholestatic liver disease: grade 1: portal changes; grade 2: periportal changes; grade 3: septal changes; grade 4: cirrhotic stage(10).

Progressive cholestatic liver disease remains the most problematic life threatening complication of parenteral nutrition in short bowel syndrome. The incidence in childhood is as high as 40-60%(11,12). Potential liver damaging factors are: underlying disease, lack of enteral feeding, duration of parenteral nutrition, prematurity, extrahepatic biliary obstruction, recurrent sepsis, hypercaloric parenteral nutrition, lipid substitution > 1 g/kg body weight/day.

It is under discussion whether there is correlation between the incidence of liver disease in SBS and the underlying disease. Several studies showed a higher prevalence of liver disease in SBS compared to other causes of intestinal failure(9,11,12). It has been suggested that liver disease is less frequently associated with medical causes of intestinal failure than with surgical causes except for such cases with protracted diarrhea that show a very aggressive form of intestinal failure. In surgical SBS the length of the bowel influences significantly the development of chronic liver failure, but that is potentially dependent on the possibility of enteral nutrition. It is evident that in patients with a surgical SBS a history of multiple surgical interventions and septic periods negatively influences the prognosis. But on the long term, underlying diseases that make PN difficult to control such as diseases of protracted diarrhea show the tendency of developing PN associated liver disease more quickly.

Another important factor is the lack of enteral feeding, which is directly associated with the intensity of parenteral feeding. Total PN reduces the secretion of several gastrointestinal hormones, such as gastrin, motilin, pancreatic polypeptide, insulinotropic polypeptide and glucagon. The lower level of these hormones may lead to a reduction of motility and increases bacterial overgrowth and promotes biliary stasis (13). Therefore, it is very difficult to differentiate whether the increased risk of liver dysfunction is caused by the absence of enteral stimulation or the effects of PN. But generally enteral feeding has some important protective aspects that work without the influence of PN. It also has been suggested that the mucosal atrophy induced by the lack of enteral nutrition allows increased bacterial translocation across the gut mucosal barrier, but the results of clinical studies did not show evidence for that fact (14,15).

In addition, the absence of enteral nutrition could lead to a reduction of enterohepatic circulation and accumulation of toxic bile acids with subsequent cholestasis(16).

One of the first risk factors detected for parenteral-nutrition associated cholestasis is the relation between prematurity and liver damage. In infants with a birth weight below 1000 g the incidence for cholestatic liver disease increases substantially. Beate et al. detected a incidence of

liver damage as high as 50% in infants with weight <1000 g and only 10% in infants >1500 g (17). Regarding the histology in neonates intrahepatic cholestasis is more common than steatosis hepatitis, maybe reflecting the immaturity of the biliary excretion system in neonates and its susceptibility to hypoxia. It is also known that the bile salt pool in premature infants is reduced. There is a diminished hepatic uptake and synthesis of bile salts and additionally a reduced enterohepatic circulation compared to infants and children(18). The development of cholestasis in infants is closely related to the duration of total parenteral nutrition (TPN). The overall incidence of cholestasis in infants on TPN is around 23% but increases up to 80% after 60 days and 90 % after 3 months respectively(17).

Recurrent sepsis is an important risk factor to develop intrahepatic cholestasis. Sepsis in

SBS is associated with bacterial overgrowth due to intestinal stasis. There is some evidence that the liver damage is caused by bacterial overgrowth leading to bacterial translocation, with consecutive sepsis, but is also an effect of bacterial endotoxins. The pathway leading to liver damage in recurrent sepsis is not disclosed yet, even so cytokines such as TNF- α are suspected to play an important role(19).

Another problem possibly related to bacterial overgrowth is the frequently observed development of gastrointestinal ulcerations. These ulcerations within the small bowel might impair the intestinal barrier function of the bowel mucosa. There is evidence for the fact that bacterial overgrowth reduces the normal peristalsis, worsening the situation of the bacterial overgrowth(20).

Severe protein malnutrition can be responsible for developing hepatic steatosis. Proteins are needed to synthesize very low density lipoprotein (VLDL), that is needed for the triacylglycerol (TAG) export. Patient under PN should generally be substituted sufficiently with amino acids for VLDL synthesis. Up to now, the deficiency of several methionine metabolites such as carnitin, choline, and taurine has been suggested to be responsible for steatosis and cholestasis. This is important in preterm infants, since normally methionine can be converted into these metabolites by hepatic transsulfuration, a metabolic pathway that is underdeveloped in these patients(21). Carnitine, cholin and taurine generally are not part of parenteral formulation and there is strong evidence that levels are, low in small patients depending on PN(22,23). Excess calories from glucose >8-12 mg/kg body weight (BW)/day are associated with hepatic steatosis, because total glucose potentially exceeds the maximum glucose oxidation rate(24). Generally high glucose infusion rates stimulate insulin release. High plasma insulin concentrations stimulate hepatic lipogenesis and the production of acylglycerol that goes along with inhibition of mitochondrial fatty oxidation. This process results in the accumulation of TAG within the hepatocytes. This could explain why continuous PN infusion has a higher risk for liver damage than cyclic infusion. A period of 8 hours and more without PN a day has shown to lower the risk for liver damage(25). The incidence of steatosis hepatitis is reduced when parts of the glucose energy supply is replaced by

parenteral lipid infusions. A very high parenteral lipid intake has also shown to result in hepatic complications(25).

A fat overload syndrome results in exceeded lipid administration, because of the inability to clear that amount of phospholipids and polyunsaturated fatty acids (PUFA). In multivariate analysis parenteral intake of soya bean based lipid emulsions >1 mg/kgBW/day has been shown to increase the risk for liver fibrosis, even so the exact pathophysiological mechanism is unresolved(26). Studies on the effect of composition of fatty acids on chronic liver disease in PN gave some conflicting results. On the one hand rats given a high proportion of omega-3 fatty acids led to increased hepatic fibrosis and reduction of PUFA content showed no significant difference PN induced liver disease(27). On the other hand, small case studies demonstrated significant benefits of children receiving higher amounts of fish-oil based omega-3 fatty acids(28).

Patients with SBS often have a history of multiple surgical interventions. Any kind of extrahepatic obstruction has to be avoided, since it is well-known that especially infants with extrahepatic atresia of the bile duct develop irreversible liver damage within a few weeks of age. In neonates and infants every kind of extrahepatic obstruction may worsen the prognosis for PN induced liver disease. In older patients there is a high risk for developing biliary sludge and gallstones.

Therapeutic goals in patients with SBS and liver disease

Bacterial overgrowth

In patients having problems with the enteral feeding, despite a sufficient bowel length, endoscopy can help to set the diagnosis of chronic bacterial overgrowth. Typically ulcerations in the small bowel appear, while the big bowel mucosa has a regular endoscopic and histological appearance. Often the significance of the bacterial overgrowth is not completely understood by the treating physicians. The culture of stool rarely shows pathogenic alterations in those patients. In those patients with typical ulcerations diagnosed by endoscopy an eradication therapy with a large variety of antibiotics can be attempted. As a first line non-resorbable antibiotics, such as paromomycin and vancomycin as a mono therapy can be administered. Some patients have a cycle of eradication therapy of one week every month. Additional antibiotics like metronidazole or cephalosporine derivatives are sometimes helpful; in some patients a combination therapy is mandatory. On the long term some patients develop bacterial overload with resistant bacteria. In those cases eradication has to be performed, according to the culture and antibiotic testing, as a life threatening problem can develop.

Enteral feeding

One of the key points in the management is the maximizing enteral nutrition. The general question is what kind of diet should be administered and what could be the ideal amount. Hyperosmolaric diet leads to intractable diarrhea in short bowel syndrome. Dilated gut or bacterial overgrowth increased permeability can lead to allergic reaction to any protein in the formula.

Several hypoallergenic formulas exist; the most frequently used are the protein hydrolysate formulas such as Pregomine® (Milupa, Friedrichsdorf, Germany) or Alfare® (Nestle, Vevey, Switzerland). The proteins in this category are hydrolyzed and have very low allergenicity. To minimize the potential risk for food allergy, it is possible to use an amino acid formula such as Neocate® (Pfrimmer Nutritia Germany, Erlangen, Germany). Concentrations of the nutrient agent and the amount of enteral nutrition have to be adapted slowly over weeks until a bowel movement frequency of 5-8 stool/day. In patients who do not tolerate sequential feeding, it may be necessary to start continuous feeding via feeding pump. When the infants get older, the diet remains the same, but it is possible to give them some additional food. Which kind is tolerated best is not predictable. Generally the children prefer salty food, due to the high loss of electrolytes in SBS. Nutrition rich in carbohydrates always has the risk of developing lactate acidosis, but it is possible to allow patients carbohydrates and sugar in a moderate amount. It is important to start with a nutrition rich in fibers, especially in patients with a preserved colon. In addition to the general ability to absorb short-chain fatty acids derived from bacterial fermentation, patients with SBS show an adaptation to the colonic mucosa too. The significant increase of brush border enzymes in the colonic mucosa allows the active transport of peptides too and potentially a transport of carbohydrates. To increase the enteral caloric intake, the supplementation of the regular food with medium chain triglycerides (MCT) can be tried, but often patients show severe diarrheal after supplementation with MCT oil. The optimal nutrition cannot be recommended for all patients but has to be tried in every patient. One goal in enteral feeding is to achieve a stool frequency that should not exceed five bowel movements/day.

Adjustment to parenteral nutrition

Since most of the patients receiving home parenteral nutrition continue to eat, it is necessary to estimate enteral energy absorption and to adapt the parenteral energy substitution in patients with SBS and PN. The US and UK guidelines suggest a total daily energy intake of 105-146 kJ/kg BW and a protein intake of 0.8-1.5 g/kg BW(29).

The doses and type of parenteral lipid infusion seem to be of great importance. In patients without enteral caloric intake, parenteral lipid infusion is necessary to prevent fatty acid deficiency.

US guidelines suggest that parenteral lipid infusion should supply 20-30% total energy and daily intake should be <2.5 g/kg BW and ideally <1.5 g/kg BW, according to the clinical guidelines of the National Institute for Health and Care Excellence (NICE) 2006. Most authors prefer a low-dose lipid regime with a daily intake of 1 g/kg BW and less. In patients with signs of progressive cholestatic liver disease, the lipid intake is reduced to one week with 1 g/kg BW and lipid dissolved vitamins are substituted. This regime has to be performed over a period longer than eight weeks.

Generally soya bean-based lipid intake is avoided, since the potential toxicity has been shown. Alternatives to the soya bean lipid infusions are lipid emulsions containing a mixture of long-chain and medium-chain TAG (e.g. Lipofundin®; B Braun, Melsungen,

Germany) emulsions with a high mono unsaturated fatty acids content (Clinoleic®; Baxter, Maurepas, France) and emulsions containing fish oil (SMOF Lipid; Fresenius Kabi, Bad Homburg, Germany).

Cyclic parenteral nutrition

Continuous PN showed to aggravate liver dysfunction. A cyclic parenteral nutrition seems to improve liver function and reduce insulin levels(25). The recommended 8-hour interruption is not always possible in practice. But in infants and small kids it is advisable to start with a 5-hour interruption of parenteral nutrition. Beside liver function, the cycled PN allows greater patient freedom with patients going to the kindergarten and school and, therefore, it is an important point to improve quality of life of our small patients and their parents(25).

Pharmacological treatment

Ursodeoxycholic-Acid (UDCA) is a naturally occurring hydrophilic bile acid formed in liver and intestines. It stimulates biliary flow, reduces cholesterol absorption and hepatic cholesterol synthesis. In neonates it has been shown to reduce duration of PN induced cholestasis and to improve liver function. The recommended dose in orally administered UDCA is 10 mg/kg BW(30). Some studies, however, show a rebound cholestasis after withdrawal of UDCA(31). In older patients the beneficial effect seem to be less evident and the side effects are more common, especially diarrhea(32).

Surgical options

Since Bianchi (33) established the longitudinal intestinal lengthening and tapering (LILT) for the first time in 1980, several centres presented their series(34). LILT has become a serious option for patients with SBS and their adaptation reaction, such as increasing the bowel diameter. Kim et al. (35) presented in 2003 a less difficult and faster to perform surgical procedure in order to increase bowel length and to reduce the diameter of the dilated bowel: the technique of serial transversal enteroplasty. Both techniques allow to wean patients with SBS from parenteral feeding(36). Therefore, they play a crucial role in the treatment of SBS, in form of gastrointestinal rehabilitation(37). LILT means dividing the entire bowel longitudinally along the antimesenteric and mesenteric border between the mesenteric vessels passing to each hemisegment. With this technique maximal tailoring and lengthening can be achieved. The hemisegments are reconstructed to new bowel loops around the half of the original diameter in an isoperistaltic manner. The bowel continuity is completed by anastomosis to the duodenum and colon. The longitudinal sutures can be performed by hand or stapler suture. The serial transverse enteroplasty (STEP) procedure is a easier surgical technique to perform. STEP means the serial transverse applications of a stapler from opposite directions, to create a zig-zag channel. Main advantage of this technique is that no anastomosis has to be

done and that there is a much lower risk of ischemic complications compared to the LILT.

Several other techniques have been performed until now but only these two techniques have proven to be beneficial for the patients in larger series. Regarding the surviving time of patients with SBS, the patients undergoing autologous gastrointestinal reconstruction seem to have a much more favourable outcome compared to the patients who did not undergo LILT. Some series have a long-term follow-up, lasting over 80 months, with a survival rate of 77%(36). Most of the patients were able to participate in normal social life, that means they went regularly to kindergarten or school. The most significant parameter for the prognosis after LILT has been shown to be the possibility to get weaned from parenteral nutrition. Beside the bowel length, the presence of the major part of the large bowel has been shown to be significant too. Up to now the decision upon which technique has to be used depends on the center of treatment. Anyway, STEP can be performed in patients after intestinal lengthening (STEP or LILT) as a second step operation, when adaptation leads to a new dilatation of the short bowel. LILT leads to a more effective lengthening compared to STEP, but it is technically more difficult to perform, with a higher risk of complications. LILT is, therefore, performed as first choice treatment only in those patients with a very short bowel and a significant dilation. STEP technique can be performed after LILT and a secondary dilation of the bowel(34,36,37).

Intestinal transplantation

Due to the difficulties of graft rejection, the intestinal transplantation has been unsuccessful until the 1990s, when first clinical series were reported. Now there are over 60 centers worldwide that perform intestinal transplantation, with over 1 200 procedures performed so far(38). At the beginning intestinal transplantation was developed to rescue patients with intestinal failure having life threatening complications from PN.

Nowadays, patients with intestinal failure due to SBS should be referred for intestinal transplantation before irreversible liver damage develops. In patients with irreversible liver damage a combined intestine/liver transplantation has to be performed. The criteria used to determine when combined transplantation is suggested are not clearly defined yet. The functional outcome of the transplanted patients shows that 70-80% of patients who undergo successful transplantation can be completely weaned from PN(38). The major problem of intestinal transplantation remains the acute and chronic rejection and immunosuppressive therapy. Acute cellular rejection can occur at any time, but is most common in the first year. Acute rejection is the leading cause of graft loss and happens in up to 79% of all patients. Infections in intestinal transplanted patients are also common, since immunosuppression is very intensive in these patients. Especially viral infections such as Cytomegalovirus have been a major problem. Secondary malignancies to the posttransplant lymphoproliferative disorder are described in 7% of all transplanted patients. The overall outcome of all patients after intestinal transplantation has been improved

dramatically in the last 10 years. The one year patient survival now is over 80%(38).

Prognosis of intestinal failure associated liver disease

Generally progressive cholestatic liver disease is considered to be irreversible beyond the early stages of cholestasis, particularly in the presence of any degree of fibrosis in the liver. But only very few data are published about the outcome of non-cirrhotic liver injury. Patients with already morphologic liver damage, such as higher degree liver fibrosis, experience functional and biochemical liver recovery, even if the perioperative risk for patients with high grade liver fibrosis is significant elevated. The liver function improvement appears to parallel autologous gastrointestinal reconstruction and a significant improvement of enteral

feeding. Histological follow-up after autologous gastrointestinal reconstruction has not been performed yet.

None of the different studies allows any comment on the possibility of histological recovery of the liver if enteral autonomy remains sustained in the long term. Older data suggest that in the presence of established fibrosis in the liver, some ultrastructural changes persist even if biochemical recovery occurs(39).

The results from different transplantation centers suggest that enteral autonomy from PN, accompanied by a program to reduce risk factors for liver dysfunction, may allow the possibility of liver function biochemical recovery(40).

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