* PEDIATRIC LIVER TRANSPLANTATION *

ESSAY

Submitted For Partial Fulfilment

Of Master Degree In General Surgery

By

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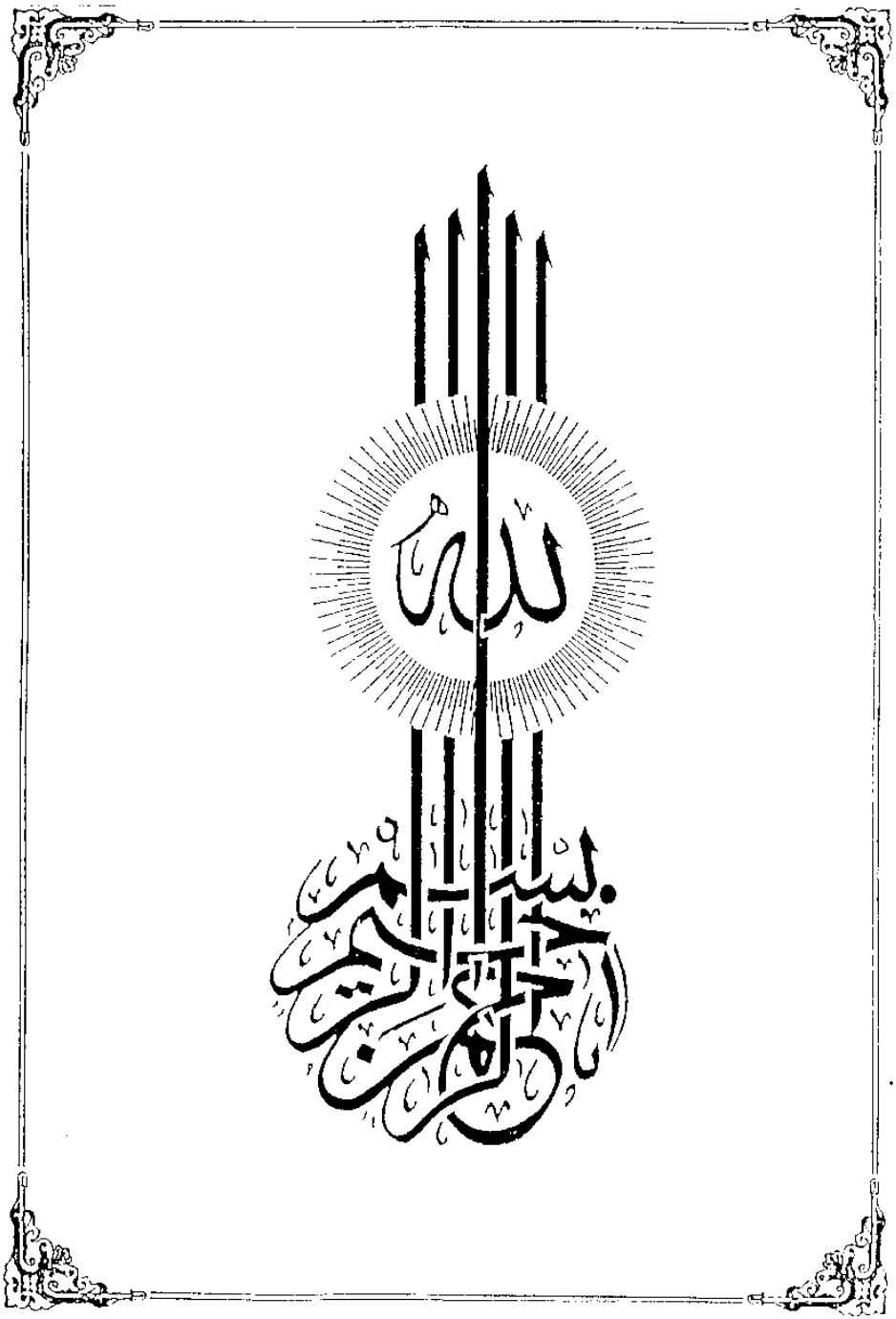
1992

TO MY FAMILY



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Acknowledgment

It is a great honour to express my deepest gratitude and appreciation to Prof. ALAA ISMAIL, Professor Of General Surgery, Faculty of Medicine, Ain Shams University for granting me the privilige of working under his supervision. I truely appreciate his instructive guidance and constructive criticism.

I am also greatly indebted to Dr. HELMY EL-GHOR, Lecturer in General Surgery, Faculty of Medicine, Ain Shams University for his close meticulous supervision, continous support and kind help throughout this work.

The Candidate

* INTRODUCTION *

Pediatric liver transplantation with reduced size donor organs (RLT) has evolved into a standard clinical procedure, increasing the choices of recipients for their treatment. Nevertheless, organ availability remains a major problem. Alternatively, hepatic segments transplantation from living related donors (RLT) has started three years ago.

In this piece of work, we will discuss first the indications of pediatric liver transplantation and the preoperative assessment of recipients and donors.

Then, the differences between reduced size transplantation (RLT), split liver transplantation (SLT), and living related donor transplantation (LRT) will be discussed. An account on the immunosuppresive therapy used for pediatric liver transplantation will be mentioned.

Finally, the complications of pediatric liver transplantation and their management will be discussed.

Pediatric liver transplantation is now considered a life saving procedure for terminal liver states aided by advances in immunosuppresive therapy and surgical techniques. We hope that this material will initiate the first step in the organization of an Egyptian programme for pediatric liver transplantation.

INDICATIONS

- A Pediatric Perspective on Liver Transplantation :-

We are entering the era where most neonatal and pediatric liver diseases can be diagnosed. Unfortunately, the medical therapeutic options remain primarily corticosteroids and penicillamine, with more major advances limited to dietary fine tuning in certain rase metabolic disorders. (1) Furthermore, the management of the debilitating symptoms of many cholestatic disorders remains supportive despite advances in the understanding of their pathophysiology. An increase in longevity has been achieved for certain structural diseases such as biliary atresia with improved surgical techniques, however, most of these efforts are temporizing maneuvers (1).

Nevertheless a cure of pediatric liver disorders is presently obtainable because the surgeons have overcome the major technical obstacles of liver transplantation and cyclosporine A has made the management of rejection easir. Unfortunatly, the persisting major limiting factor remains the shortage of donor livers (1).

So, recent advances in immunosuppressive therapy and surgical techniques, have brought liver transplantation from an experimental procedure without practical importance to a firmily established, widely applied, effective therapeutic option for pediatric patients with fulminant hepatic failure and end stage liver disease. The emergence of orthotopic liver transplantation (OLT) as a life saving procedure for infants and children with various forms of acute and chronic liver diseases has offered great benefit to the recipients (Table 1) by removing a damaged organ and replacing it with a functioning allograft. However, this gain is not without risk (Table 2) (2).

Table (1). Potential benefits of (OLT) to the pediatric - aged poplutation.

1. Replacement of the damaged organ with reversal of the pathophysiologic derangment.
2. Establishment of growth beyond limits imposed by liver disease.
3. Alteration of the phenotypic expression of the metabolic disease to a normal one.
4. Removal of the potential for the development of hepatocellular carcinoma.
5. Improvment in the quality of life.

Table (2). problems related to (OLT) in the pediatric - aged peopulation.

1. Suppression or interference with immune response espicially in children who have not had immunizations or broad infectious experience.
2. Shortage of suitable donors and the need for size-matched organs in children.
3. The effect of steroids on the growth of children.
4. The effect of (OLT) and hospitalization on social and psychological status.

* **INDICATIONS** For pediatric Liver Transplantation :-

Stated in broad terms, an infant or child should be considered for candidancy as a transplant recipient if any of the general conditions listed in Table (3) are present. (2). The specific indications for which (OLT) has been carried out in the pediatric age-group, are shown in Table (4). (2,3).

Table (3) General indications for liver transplantation.

1. Progressive end-stage Liver disease.
2. Stable Liver disease with known lethality.
3. Fatal hepatic - based metabolic disease.
4. Metabolic diseases correctable by liver cell replacement.
5. Social invalidism.

Table (4). Compilatation of specific indications for liver transplantation in pediatric population (2,3).

(I) Metabolic Diseases :-

(1) Alpha - 1 - Antitrypsin dificiency.
(2) Tyrosinemia.
(3) Glycogen storage Disease Type II.
(4) Wilson Disease.
(5) Perinatal Haemochromatosis.
(6) Crigler Najjar Type 1.
(7) Homozygous Hypercholesterolemia.
(8) Urea cycle enzyme deficiency.
(9) Primary Hyperoxaluria.
(10) Protoporphyria.
(11) Haemophilia A.

(II) Acute and Chronic Hepatitis :-

(A) Fulminant Hepatic Failure :-
1- Acute viral hepatitis.
2- Toxin or drug induced.

(B) Chronic Active hepatitis :- (cirrhosis)
1- Hepatitis B.
2- Hepatitis C.
3- Autoimmune.
4- Idiopathic.

(III) Intrahepatic Cholestasis :-

(1) Idiopathic Neanatal Hepatitis.
(2) Nosyndromic bile duct paucity.
(3) Syndromic bile duct paucity (Alagille)
(4) Familial intrahepatic cholestasis (Byler)
(5) Zellweger syndrome.
(6) Benign reccurent.
(7) Microfilament Dysfunction.
(8) Inborn errors of bile acid metabolism.

(IV) Obstructive Biliary tract Disease:

1- Extrahepatic Biliary Atresia.
2- Sclerosing Cholangitis.
3- Post - Surgical and Other traumatic biliary tract disease.

(V) Tumours :-

1- Hepatoblastoma.
2- Hepatocellular Carcinoma.
3- Sarcoma.
4- Hemangioendothelioma.

(VI) Miscellaneous :-

1- Congenital Hepatic Fibrosis.
2- Caroli Disease.
3- Budd - Chiari Syndrome.
4- Cirrhosis 2ry to prolognged TPN.
5- Cystic Fibrosis.

So, it becomes important to identify children with the greatest likelihood of progressing to sudden hepatic insufficiency, because the waiting period for liver transplantation candidates may be as long as a year, particularly in small children, or those with blood type (o). (1). Intuitively, serious consideration to place the child high on the active transplant list is needed when evidence of decreased hepatic synthetic function is present. (4-6). These criteria include (1) low coagulation factor production (for example, factor v) causing prolongation of the prothrombin time, (2) decreased ability to conjugate bilirubin levels resulting in elevated total and indirect bilirubin, (3) low serum albumin levels and/or resultant ascitis, and (4) decreasing cholosterol levels in end - stage cholestatic disorders. (1).

*** CONTRAINDICATIONS for (OLT) in pediatric patients :-**

There are several conditions which are considered to constitute a contraindication to OLT, these are listed in Table (5). (2).These contraindications which are listed as being absolute or relative (high risk) will change with time and may need to be modified by each individual center. However, each of these conditions should be carefully sought out and considered for every potential candidate.

Table 5. Contraindications to liver transplantation.

(A) Absolute contraindications :

1- Primary extrahepatic unresectable malignancy.

2- Malignancy metastatic to the liver.

3- Progressive or terminal non-hepatic disease (HIV infection).

4- Untreated infection.

5- Portal vein thrombosis.

(B) Relative contraindications :

1- Previous portocaval shunting operation.

2- Infection.

3- Family/child inability to understand or to comply.

(I) Metabolic Diseases of the liver :-

Because the liver plays a central role in synthethic, degradative, and regulatory pathways involving carbohydrate, protein, lipid, trace elements, and vitamin metabolism, there are many metabolic abnormalities or specific enzyme deficiencies that affect the liver primarily or secondarily. Liver disease may arise when absence of an enzyme produces a block in a metabolic pathway. When unmetabolized substrate accumulates proximal to black, deficiency develops of an essential substance, or synthesis of an abnormal metabolite occurs.

The specterum of pathologic changes includes : (1) Hepatocyte injury, with subsequent failure of metabolic functions, often eventuating in cirrhosis or liver tumours or both; (2) Storage of lipids, glycogen, or other products; (3) absence of structural change despite profound metabolic effects, as with urea cycle defects. The clinical manifestations of metabolic liver diseases mimic infections, intoxications, and haematologic and immunologic diseases. (Table 6) (7).

Table 6. Clinical Manifestations that suggest the possibility of metabolic liver disease.

- Jaundice, hepatomegaly (± splenomegaly), fulminant hepatic failure.
- Hypoglycaemia, organic acidemia, hyperammonemia, bleeding (coagulopthy).
- Recurrent vomiting, failure to thrive, short stature, dysmorphic features.
- Developmental delay, psychomotor retardation, hypotonia, progressire neuromuscular deterioration, seizures.
- Cardiac dysfunction, failure, unusal odours, rickets, cataracts.

Further clues are provided by family history of a similar illness, but in most cases, clinical and laboratory evidences will guide the evaluation. Livre biopsy offers morphologic study and will permit enzyme auays, as well as quantitative and qualitative assays of various other contituents.

Liver transplantation is a therapeutic option for some metabolic disorders in which the deranged metabolic process is predominantly hepatic - based and the tissue damage is confined to the liver. In some cases it may be necessary to transplant both the liver and other organs damaged by the , mtabolic dynfunction. For example, primary hyperoxaluria affecting the kidneys, and familial hypercholesterolemia with cardiac involvment, may require dual organ transplantation (2). Many metabolic diseases are amenable or patentially imporoved by liver transplantation. (Table 4). In addition the malignant potential of these diseases necessitates careful monitoring and early transplantation before malignant degeneration occurs. (7).

Alpha - 1 - Antitrypsin Dificiency :- (∝ - 1 - AT. deficiency)

Death from ∝- 1 - antitrypsin deficiency - associated liver disease may occur as early as 9 monthhs of age. About half of the patients with cirrhosis die during the first l0yr of life (8). ∝ - 1 - antitrypsin a serum antiprotease, which is produced primarily in the liver, is thought to be important in the inactivation of proteolytic enzymes released from dead bacteria or leukocytes in the lung and liver. Deficiency of the∝- 1 - AT., leads to accumulation of these enzymes, proteolytic destruction of pulmonary tissue and development of emphysema.

In the liver, a small percentage of individuals homozygous for deficiency of ∝- 1 - AT., the major serum protease inhibitor, will have neonatal cholestasis and later childhood cirrhosis. (7).The most common allele of the protease inhibitor (Pi) system is "M", and the normal phenotype is "PiMM". The "Z" allele predisposes to clinical deficiency, patients with liver disease are usually "PiZZ" and have serum∝- 1 - AT. levels less than 2 mg/ml (10 - 20 % of the normal).

The incidence of "PiZZ" phenotype is estimated at 1 : 2,000 - 4,000. Of all the "PiZZ" persons, less than 20 %. will develop neonatal cholestasis (7). These patients are indistinguishable from other infants with "idiopathic" neonatal hepatitis, of whom they constitute approximately 5 - 10 %. In affected persons, the course of liver disease is highly variable. Jaundice, acholic stools, and hepatomegaly are present during the 1st wk of life, but the jaundice usually clears during the 2 nd - 4 th month. There may follow complete resolution, persistant liver disease, or the development of cirrhosis. In older children, chronic liver disease or cirrhosis, with evidence of portal hypertension may appear. (7).

The diagnosis is best made by determination of α-1-AT. (Pi) phenotype and confirmed by biopsy. PAS - positive diastase - resistant intracytoplasmic globules are seen in periportal hepatocytes. Immunoflurescence and immunocytochemical studies have shown this material to be antigenically related to α-1-AT. Liver transplantation in these children leads to the acquisation of the donor phenotype, normal circulating levels of α-1-AT., and pulmonary diseases may be avoided, or if present may stabilize or regress. (9).

- The indications for liver transplantation evaluation in these children include:

(a) cholestasis during infancy that does not recede, (b) recurrence of jaundice, and (c) deteriorating coagulation studies. Indications of early transplantation are designed to not only prevent chronic lung discase, but to ensure intervention before the development of physiologic cyanotic pulmonary arteriovenous shunts or chronic renal disease secondary to a specific immune - related glomerulonephritis. (10,11). Both these complications occur more frequantly in this particular liver disease.

Tyrosinemia :-

Tyrosine obtained from ingested protein and synthesized endogenously from phenylalanine, is used for protein synthesis and is a precursor of dopamine,

norepinephrine, epinephrine, melanin, and thyroxine. Excess tyrosine is metabolised to carbon dioxide and water. At least two distinct clinical entities are associated with a persistent increase in plsama concentrations of tyrosine, but only in tyrosinemia type II are signs and symptoms attributed to high levels of tyrosine in body fluids. In hereditary tyrosinemia type I the causal relationship with increased tyrosine levels remain unclear (7). A transient from of tyosnemia is seen in newborn infants as well.

Tyrosinemia Type I (Tyrosinosis, Hereditary Tyrosinemia, Hepatorenal Tyrosinemia).

In this condition, caused by a deficiency of the enzyme "fumarylacetoacetate hydrolase", a moderate elevation of serum tyrosine is associated with sever involvment of the liver, kidney, and central nervous system. These findings are thought to be due to an accumulation of intermediate metabolites of tyrosine in the body, specially succinylacetone. (7). Clinically, there are two main forms of the disease, the neonatal or acute form which comprises most reported cases, and the chronic or latent form.

Intermediate forms also occur. Acute and chronic forms have been observed within the same family as tyrosinemia type I is an autosomal recessive trait. Most reported patients have a French - Canadian ancestry. The prevelance of the condition is estimated to be 1 in 12,000 in the French - Canadian population of Quebec (7). Prenatal diagnosis has been achieved by measurement of succinylacetone in ammniotic fluid and by the enzyme assay in chorionic villus biopsy.

Infants having the "Acute Form" become symptomatic within the first 6 mo of life. Failure to thrive, developmental delay, irritabilty, vomiting, diarrhea, and fever are among the early manifestations. Hepatomegaly. Jaundice, hypoglycemia and bleeding tendencies as manifested by melaena, haematuria and ecchymosis are common findings. A cabbage like odour of some infants is related to metabolites methionine. Death hepatic failure occurs before the 2nd yr of life.