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EDITORIAL

Challenges in childhood liver transplantation in innate errors of metabolism☆

Desafíos del trasplante hepático infantil en los errores innatos del metabolismo

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Liver transplantation is a procedure that has been used regularly for treatment of children with terminal liver disease for decades, with evidence over this long period of excellent outcomes in terms of patient and graft survival.

In this time, some of the challenges specific to transplantation in children compared to adults have been overcome, such as challenges involving surgical technique, including the need for specialised paediatric surgeons and the low availability of paediatric donors (which has led to the development of alternative surgical techniques, such as split donation or living donor transplantation), or the need for improved severity scoring systems for liver failure to guide the prioritisation of patients in the transplant list.

In most cases, paediatric patients included in the liver transplant list have cholestatic liver disease diagnosed in the first weeks or months of life that progresses to biliary cirrhosis and chronic liver failure, although chronic liver failure of other aetiologies can also develop at later ages.

However, in some instances we face devastating situations such as acute liver failure, which is concerning both in terms of diagnosis and the approach to its management, as it often manifests with a very rapid onset of severe liver failure that may be difficult to identify based on the clinical presentation due to similarities with other life-threatening conditions with systemic manifestations where the liver is not the source of the problem but just one of the involved organs.

Acute liver failure is the second most frequent indication for liver transplantation in most published paediatric case series, and once the diagnosis is established, the most important task is to determine its aetiology,[1] and whether it can be treated medically or requires urgent liver transplantation to prevent a dire outcome, such as the patient's death. Studies like the one published by Juan José Gilbert Pérez, Belén Jordano Moreno and Mónica Rodríguez Salas in this issue of Anales de Pediatría[2] tackle the need to establish an aetiological diagnosis and the possibility of developing prognostic scoring systems to help make the best possible therapeutic decisions in this devastating situation, considering that the liver is the only visceral organ capable of regeneration.[3]

Inborn errors of metabolism constitute the third most frequent indication for liver transplantation in paediatric patients; they usually manifest in the first months of life[4] and are associated with substantial morbidity and mortality. They are a heterogeneous group, with courses of disease that may be similar to that of cholestatic disease, or have a sudden and severe onset, similar to acute liver failure and requiring urgent liver transplantation, both of them situations that are indications for transplantation that are nearly exclusive to the paediatric population.

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Hepatic-based inborn errors of metabolism, whose commonality is the presence of enzyme deficiencies, may be classified based on the type of liver dysfunction they cause.

Thus, there is a first group in which the synthetic function of the liver is impaired, leading to—as occurs in most indications for transplantation—cirrhosis and potentially development of a malignant tumour in the cirrhotic tissue. This group of hepatotoxic metabolic diseases of the liver includes Wilson disease, tyrosinaemia type 1 or alpha-1-antitrypsin deficiency. Patients with these diseases may develop complications characteristic of cirrhosis, and the timing of transplantation could be determined based on the PELD or MELD score. Transplantation may also be indicated on an urgent basis if the patient develops acute liver failure or malignancy.

There are other metabolic disorders where the liver is the site of the defect but the effects are not hepatotoxic. These are usually caused by a specific defect in the synthesis of a liver protein, such as Crigler-Najjar type 1, haemophilia A or hyperoxaluria. In other diseases, the genetic defect is expressed in other organs and not exclusively in the liver, giving rise to systemic illness, as occurs in organic acidaemias.

In these two last groups of non-hepatotoxic metabolic disorders, the clinical manifestations are extrahepatic, and the associated metabolic toxicity may give rise to severe complications—neurologic, cardiovascular or in other organs and systems, as is the case in urea cycle disorders or homozygous familial hypercholesterolemia. In these patients, liver transplantation can correct the enzymatic deficiency, preventing the noxious impact of the metabolic disorder. Consequently, decisions regarding transplantation and its timing cannot be based solely on the assessment of the synthetic function of the liver or the development of complications of cirrhosis, but must also consider the prevention of potential complications that may pose a risk to the life of the patient or cause permanent damage to other organs.

Unfortunately, the particular indication for transplantation of non-hepatotoxic hepatic-based metabolic disorders is not currently considered in the established protocols for prioritisation. In some cases it is also difficult to determine the ideal timing of transplantation, as a choice needs to be made between long-term dietary restriction and performance of a surgery that is not without risks, even if most paediatric case series report 1-year survival rates greater than 90% for liver transplantation.

The challenge of determining whether transplantation is indicated is further complicated when children present with acute liver failure and a metabolic aetiology is strongly suspected. The onset of such disorders in the form of acute liver failure is analysed by Filipa Dias Costa in the study published in the current issue of Anales de Pediatría.[5] These presentations are usually extremely severe and pose a significant challenge to decisions regarding transplantation, as the aetiological diagnosis is usually very complex but there is little time for its investigation, and liver transplantation is not curative in all inborn errors of metabolism.

The decision to perform transplantation under these circumstances is also influenced by the scarcity of donors. As a consequence, in addition to optimising the use of available grafts by surgical techniques such as reduction of an adult donor graft, and especially the split liver technique, transplantation from living donors is now also being used. The experience in the 1990s, especially in Asian countries, has confirmed that it is possible to use grafts from heterozygous donors in most liver transplantations in patients with metabolic disorders. This should always be done after verifying that the enzymatic activity of the heterozygous donor is sufficient for correct metabolic functioning in both the recipient and the donor.

Other options developed in recent years are auxiliary transplantation, which consists in transplanting the whole or a partial left lobe of a living or deceased donor while conserving the right lobe of the recipient. This procedure, while technically complex, allows the native liver that functions normally aside of the enzymatic defect to serve as a safety net should the graft fail to function post transplantation. Another advantage is that auxiliary transplantation could serve as a bridge to gene therapy, should it be developed in the future. Our unit has pioneered this type of transplant in Spain, performing transplantation of a graft from the mother in a girl with ornithine transcarbamylase deficiency.

We ought to conclude highlighting that knowledge of the natural history and prognostic factors of different liver diseases is essential to determining the indication for and timing of liver transplantation correctly. In acute liver failure, the acuity and outcome of patients are influenced by the early recognition and referral to a specialised centre, where different diagnostic and therapeutic possibilities need to be considered in a short timeframe. Inborn errors of metabolism should always be considered in the differential diagnosis, especially in young infants, differentiating them from other equally severe presentations where liver transplantation is contraindicated.

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