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 pediatric surgeons and the low availability of pediatric 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, pediatric 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, 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 Rodriguez Salas in this issue of Anales de Pediatría 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.

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 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 com-
mmonality 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 func-
tion 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 tis-
te. 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 aci-
daemias.

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 disor-
ders or homozygous familial hypercholesterolemia. In these
patients, liver transplantation can correct the enzymatic
deficiency, preventing the noxious impact of the metabolic
disease. 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 pre-
terior 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 transplan-
tation of non-hepatotoxic hepatic-based metabolic disor-
ders 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 perfor-
amance 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 sus-
pected. 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. These presen-
tations 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
curate in all inborn errors of metabolism.
The decision to perform transplantation under these cir-
cumstances is also influenced by the scarcity of donors. As
a consequence, in addition to optimising the use of avail-
able 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 heterozy-
gous donors in most liver transplantations in patients with
metabolic disorders. This should always be done after veri-
fying 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 func-
tions normally aside of the enzymatic defect to serve as a
safety net should the graft fail to function post transplan-
tation. Another advantage is that auxiliary transplantation
could serve as a bridge to gene therapy, should it be de-
veloped 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 fail-
ure, the acuity and outcome of patients are influenced
by the early recognition and referral to a specialised cen-
tre, where different diagnostic and therapeutic possibilities
need to be considered in a short timeframe. Inborn errors
of metabolism should always be considered in the diffe-
rential diagnosis, especially in young infants, differentiating
them from other equally severe presentations where liver
transplantation is contraindicated.

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