HEPATIC-BASED INBORN ERRORS OF METABOLISM

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ABSTRACT

Inborn errors of metabolism (IEMs) are a vast, diverse, and heterogeneous set of genetic disorders. Hepatic-based IEMs are a significant cause of morbidity and mortality, and represent a common indication for liver transplantation (LTx) in the paediatric population. This review focuses on four of the most common hepatic-based IEMs where Tx, either as whole organ liver or as isolated hepatocytes, may be an option: familial amyloid polyneuropathy, Wilson’s disease, alpha-1 antitrypsin deficiency, and phenylketonuria.

Keywords: Inborn errors of metabolism, inherited metabolic disorders, liver transplantation, hepatocyte transplantation, gene therapy.

INTRODUCTION

Inborn errors of metabolism (IEMs) are a vast, diverse, and heterogeneous set of genetic disorders that are caused by alterations of a specific chemical reaction in metabolism. The term was coined by Sir Archibald Garrod in 1902.1 Although individually rare, IEMs are collectively common with an estimated incidence >1:1,000.2 There are hundreds of different IEMs mapped to date, and the number will probably continue to grow until all variants of enzymes and transporters that specify homeostatic mechanisms in humans are identified.3,4 IEMs are a significant cause of morbidity and mortality, especially in childhood. A vast number of key metabolic reactions occur in the liver. This review focuses on the most common hepatic-based IEMs where transplantation (Tx), either as whole organ or as isolated hepatocytes, may be an option. Based on data from the European Liver Transplant Registry, familial amyloid polyneuropathy (FAP), Wilson’s disease (WD), and alpha-1 antitrypsin deficiency (A1ATD) combined accounts for ~55% of all liver transplants for IEMs (Table 15-13). In phenylketonuria (PKU), due to its relative frequency, arduous management, and grave complications, hepatocyte transplantation (HTx) is being investigated14.

Table 1: Hepatic-based inborn errors of metabolism (IEMs) and liver transplantation in Europe from 1988-2009.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Incidence</th>
<th>No. of transplants performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial amyloid polyneuropathy</td>
<td>1:500 to 1:100,0006,6</td>
<td>12807</td>
</tr>
<tr>
<td>Wilson’s Disease</td>
<td>1:30,000 to 1:100,0004</td>
<td>8127</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin deficiency</td>
<td>1:2,000 to 1:5,0009</td>
<td>5427</td>
</tr>
<tr>
<td>Hereditary haemochromatosis</td>
<td>1:200 to 1:30030</td>
<td>4687</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>1:120,00011</td>
<td>2307</td>
</tr>
<tr>
<td>Tyrosinaemia Type 1</td>
<td>1:100,00012</td>
<td>987</td>
</tr>
<tr>
<td>Homozygous hypercholesterolaemia</td>
<td>1:1,000,00013</td>
<td>217</td>
</tr>
</tbody>
</table>

NB: Transplants for non-hepatic-based IEMs are excluded.
FAP

FAP is caused by a mutation in the gene that encodes transthyretin (TTR), and was first described by Mario Corino de Andrade in 1952. There are >100 mutations in the TTR gene associated with disease, the most common being V30M. FAP is an autosomal dominant disease found throughout the world, but not all carriers develop the disease. For example, Northern Sweden has a high carrier frequency of the V30M mutation - 1.5% of the population - but only 5% develop symptoms before the age of 40 years. In contrast, endemic areas in Portugal have ten times lower carrier frequency (0.18%), but high penetrance (87% before the age 40). Unexpectedly, homozygote carriers do not have more severe disease than heterozygotes. TTR transports thyroxin and retinol in serum and cerebrospinal fluid, and is secreted by hepatocytes. TTR is a significant plasma protein (approximately 25 mg/dl), and has a tendency to form amyloid in essentially all vascular organs. These amyloid deposits are found, to some degree, in 25% of the population older than 80 years, usually without clinical significance. In TTR V30M, a single amino acid substitution results in a structural change of the protein, causing altered metabolism and enhanced amyloid fibril formation, resulting in neuro and cardiomyocyte-toxicity at a younger age.

FAP is characterised by progressive peripheral and autonomic neuropathy or cardiomyopathy in early adulthood and results in severe disability and death within 10-15 years. It is caused by deposits of mutant TTR displacing normal cellular structures, resulting in impairment of organ function. Clinically, FAP should be considered in patients with a progressive axonal polyneuropathy of unknown origin, especially when associated with autonomic dysfunction or cardiac manifestation. Biopsy of an affected organ may then confirm the diagnosis. Family history is of paramount importance. Medical treatment options for FAP are evolving. The working hypothesis is that if one can stabilise TTR in its tetrameric form, amyloid formation may be prevented. Tafamidis, a meglumine salt, has been shown to slow the neurological deterioration in FAP, and has been approved in Europe and Japan. Another strategy is inhibition of TTR synthesis on the RNA level. Again, mainly two strategies for this exist; degradation of mRNA by antisense oligonucleotides or gene silencing using small interfering RNAs. Phase I studies for both strategies have recently been completed, and Phase II/III studies are ongoing. Both strategies appear safe, and efficiently reduce the amount of circulating TTR.

Liver transplantation (LTx) has been performed as treatment for FAP since the early 1990s. Worldwide, over 2,000 liver transplants have been registered (www.fapwtr.org), of which 1,200 have been performed in Europe alone. The overall 5-year patient survival in Europe following Tx is 76%, but 100% 10-year survival has been reported by a Japanese group. TTR is not hepatotoxic, meaning that the explanted liver from a FAP patient can be transplanted into another patient with terminal liver failure. The first such 'domino' procedure was performed in 1995. The V30M liver will indeed continue to produce mutant TTR, but the generally slow progression of the disease may justify the use in older recipients. There is mainly one drawback with LTx for FAP (aside from the necessity of immunosuppression and risks of surgery): the transplanted liver continues to produce normal TTR, which, in some patients, continues to be incorporated into existing fibril deposits, especially in the heart. Combined heart-liver Tx has been performed in patients with FAP, but is not likely to become a widely available treatment option.

WD

WD is caused by mutations in the gene encoding ATP7B, and was first described Samuel Alexander Kinnier Wilson in 1912. There are >500 mutations associated with WD in the ATP7B gene (http://www.hgmd.cf.ac.uk/ac/index.php?gene=ATP7B). WD is an autosomal recessive disorder with a prevalence of about 1:30,000 to 1:100,000, but the prevalence may be considerably higher in some areas, e.g. East Asia. Genotype-phenotype correlations in WD have yet to be established, as the number of homozygotes is exceedingly small, and the prevalence of compound heterozygotes is high. ATP7B is found exclusively in the hepatocyte and permits the efficient excretion of copper into the bile. Copper is an important cofactor for many proteins, but the average diet provides an abundance and the majority ends up being excreted. The most common effect of mutation in ATPB7 is protein misfolding. This misfolding causes altered metabolism, decreased stability, and loss of copper-transport activity. The resulting copper accumulation is toxic, especially in the...
liver and brain. Recently, it has been shown that copper is required for tumour growth and signalling in some cancers, however, the rate of hepatobiliary malignancies in WD is very low. WD is characterised by liver disease in the second decade, followed by neuropsychiatric disorders in the third decade, but the clinical presentation is highly heterogeneous and may include Fanconi syndrome, cardiomyopathy, osteomalacia, and anaemia. The median delay in diagnosis is reported to be 2 years. Clinically, a diagnostic scoring system has been developed with high sensitivity and specificity. It combines clinical findings, lab results, liver biopsy, and mutation analysis. Pragmatically, the presence of low serum ceruloplasmin and higher urine copper is sufficient to conclude the diagnosis of WD in most cases.

Kaiser-Fleischer rings are present in about 50% of cases of WD at diagnosis. Liver biopsy is used to define liver status in cases with ambiguous biochemical parameters and to evaluate hepatic copper levels with specific stains. Medical treatment of WD include copper-chelators (penicillamine or trientine) and zinc salts, with the goal to establish and maintain normal copper homeostasis. Medical treatment can generally prevent and even reverse symptoms of copper overload, at least when initiated at an early stage in the disease. However, non-responders or lack of compliance to the drug treatment may result in disease progression and acute liver failure with mortality approaching 100%. Sporadically, therapeutic plasma exchange and various forms of albumin dialysis have been reported as effective techniques for rapidly reducing serum copper levels in WD crisis, delaying or even preventing the need for LTx. HTx has been proven safe, and at least transfiently effective, in treating other IEMs, and could conceivably be utilised as support until chelation treatment shows its effect. LTx is the treatment modality of choice in most cases of WD crisis. In Europe, >800 patients with WD have been transplanted. The 5-year overall survival rate is 85%.

A1ATD

A1ATD is an autosomal recessive disease caused by mutations in the SERPINA1 gene. The disease was discovered in 1963 by Carl-Bertil Laurell. In the SERPINA1 gene there are >120 mutations identified, but the majority of patients with severe disease are homozygous for the Z mutation. A1ATD has an estimated prevalence of 1:2,000 - 5,000. Not all develop disease: it is estimated that 10-35% of patients with ZZ genotypes do not exhibit any clinical symptoms. In an epidemiological study carried out in Sweden over 40 years, <10% of the 127 infants that were identified had clinically significant liver disease over the first four decades of life. A1ATD is mainly synthesised by hepatocytes and to a small degree in the lungs. The physiologic serum concentration of A1AT for adults ranges from 1.0-1.7 g/l, but as an acute phase protein, it is up-regulated during inflammation, infection, cancer, and pregnancy. The most important function of A1AT is inactivation of released proteolytic enzymes in the lungs. In patients with the ZZ variant, A1AT proteins have a single amino acid substitution causing structural change, accumulation in the rough endoplasmic reticulum and decreased secretion. The function of A1AT is also reduced. In this sense, A1ATD is similar to the amyloidoses (e.g. FAP). As a result of decreased secretion of A1AT, overt protease activity ensues in the lungs, resulting in destruction of lung matrix components, alveolar structures, and blood vessels. Injury to liver cells also occurs, but susceptibility to disease is determined by processing abilities for misfolded A1AT. Interindividual differences in this cellular machinery are thought to be responsible for the different susceptibility to chronic liver disease. Higher rates of liver cancer are found in A1ATD due to hepatic inflammation and increased liver cell turnover. A1ATD typically appears with chronic obstructive pulmonary disease (COPD), emphysema, and disseminated bronchiectasis, usually between the forth and the fifth decade, but earlier onset may occur, especially in smokers. In younger patients there is often a long lapse before A1ATD is diagnosed, as the symptoms are attributed to a more likely diagnosis of asthma. The progression to liver cirrhosis in patients with A1ATD is usually slow. However, some patients develop early end-stage disease, with the need for LTx at a young age.

Diagnosis of A1ATD is usually made by measurement of serum A1AT concentration in combination with determination of C-reactive protein (the latter to exclude ongoing inflammation), and established with genotyping. Treatment of A1ATD lung manifestations does not differ from standard treatments of COPD. Substitution therapy with A1AT derived from pooled human plasma is performed in some European countries,
PKU

PKU is an autosomal recessive disease caused by mutations in the phenylalanine hydroxylase (PAH) gene. The disease was first described by Asbjorn Folling. In the PAH gene >500 mutations have been mapped, and most have effects on PAH activity. Established genotype-phenotype correlations are emerging. PKU has a prevalence of about 1:10,000 in Europe, but for some areas it is higher. PAH converts phenylalanine (Phe) into tyrosine, and is found exclusively in the liver. Loss of PAH activity results in increased concentrations of Phe in the blood. Phe is an essential amino acid, and its entry into the brain is mediated by the large neutral amino acid carrier L-type amino acid transporter 1 (LAT1). Two other amino acids—tyrosine (precursor of dopamine and noradrenaline) and tryptophan (precursor of serotonin), also enter the brain via the LAT1 carrier. Since they compete for the same carrier, high concentrations of Phe in the blood impairs brain uptake of tryptophan and tyrosine. Accordingly, cerebral protein synthesis rate is decreased in PKU patients when concentration of Phe is high. Furthermore, animal studies have shown that high concentration of Phe and its metabolites (principally phenyl lactate and phenylacetate) exert deleterious effects on markers of bioenergetics activity in neural tissue. Together with the deficiency of tyrosine and its downstream products, these factors may explain the neurotoxicity in PKU.

PKU is classified by the severity of hyperphenylalaninaemia. The normal range of blood Phe concentrations is 0.8–1.8 mg/dl; concentrations above 20 mg/dl denote classic PKU. Clinically, untreated PKU leads to disturbed brain development with profound retardation, microcephaly, epilepsy, and other neurologic symptoms. Most countries have a newborn screening programme, and early detection and implementation of a Phe-restricted diet widely prevents neurological symptoms. However, the diet regimen is arduous and even patients with well-controlled PKU exhibit a variety of subtle physical, cognitive, and behavioural symptoms. Perhaps unsurprisingly, it has been shown that patients with PKU spend considerably more time managing their disease than patients with Type 1 diabetes. Sapropterin dihydrochloride, a pharmaceutical form of the chaperone PAH cofactor tetrahydrobiopterin, lowers plasma Phe concentrations for up to half of patients with PKU. Responders reportedly also experience increases in Phe tolerance and increased quality of life (QoL).

One patient with PKU has received a LTx for reasons unrelated to PKU, and the patient’s blood Phe level normalised after transplant. HTx has been performed in one patient who had poor dietary control, with temporary improvement of blood Phe levels. Clinically, HTx involves isolation of hepatocytes from livers rejected for solid organ Tx, and is performed with an infusion of the cells via a portal catheter into the liver, in a manner much resembling that of islet Tx. It is minimally invasive, and generally performed under local anesthesia. In the case of PKU, the cells need only improve a single enzyme deficiency. A clinical trial with hepatocytes for PKU is currently ongoing in the United States.

CONCLUSION

Even though IEMs are regarded as simple mendelian diseases, clear genotype-phenotype correlations are rarely seen. It is increasingly recognised, partly through the advent of next-generation sequencing, that multiple causative alleles, modifier alleles, or both, are common. Hopefully improvements in our understanding of these genetic mechanisms will result in robust methods that can identify patients needing treatment before devastating symptoms occur. Gene therapy, and cellular Tx have the potential of dramatically improving the QoL of patients suffering from IEMs in the near future. For now, improved medical treatments and whole organ LTx may increasingly be considered in hepatic based IEMs.
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