Inborn Errors of Metabolism and Liver Transplantation

Susan A. Berry, M.D.
Division of Genetics and Metabolism
Department of Pediatrics
University of Minnesota

University of Minnesota
Amplatz Children's Hospital

Disclosures

- Member of the UCDC – an NIH-sponsored Rare Disease Consortium
- Investigator for clinical trials with Hyperion Therapeutics for novel ammonia-scavenging medications
- Investigator in clinical trial with Cytonet to monitor subjects treated with hepatocyte infusions for urea cycle disorders

What are inborn errors of metabolism ?

- Genetic conditions – a person is born with the disorder
- Often autosomal recessive
  - Parents are “carriers”
  - Child is first person in family to have condition
- Genetic error is usually in an enzyme controlling a metabolic pathway
- Blockage in metabolic pathway results in accumulation of toxic material in the system

How do we find the affected person?

- Newborn screening
- Family history
- Baby gets very sick

Current treatments not involving transplantation

- Restrict the material for which there is a blockage in the metabolic pathway
  - Example: protein in disorders where ammonia accumulates
- Remove the abnormal material that accumulates
  - Example: dialysis or scavenger medications in disorders where ammonia accumulates

Kinds of metabolic conditions that affect the liver

- Liver is central to many metabolic pathways
- Needed for recycling and processing of most proteins in foods
- Needed for storing part of our body's starch supply as hepatic glycogen
- Blocks in metabolic pathways can either
  - Not affect liver function but affect the overall accumulation of abnormal metabolic products

  OR
  - Damage the liver resulting in abnormal liver function tests and eventual scarring and loss of function

Why liver transplantation in treatment of inborn errors of metabolism?

- In conditions without underlying liver damage, transplant replaces abnormal enzyme with a normal liver
- In conditions with liver-damaging byproducts transplant replaces damaged liver
  - Replaces abnormal enzyme function
  - May prevent liver cancer that can occur due to constant liver damage caused by the disorders

Why make this distinction?

- The only way to fix a badly damaged liver is to replace it – not amenable to partial corrections

- If the liver is ITSELF ok, with just a metabolic block, may only need partial correction for substantial metabolic improvement or stabilization.

Spectrum of conditions: considerations for treatments

- Medical complexity
  - Volatility – how often do episodes occur
  - Degree to which decompensation is life-threatening
- Availability of less-invasive treatments
- Does the condition cause damage outside of the liver?

RISK vs. BENEFIT!

What makes us consider early liver transplant for an IBEM?

- Is the condition so severe that it is difficult to maintain stability?
- Are treatments that are available complicated and expensive?
- Would a liver transplant stabilize or prevent further extra-hepatic consequences

(BRAIN DAMAGE)

Options in liver transplant

(Disclaimer! I am not a transplant surgeon or transplant expert!

- Orthotopic liver transplant
- Partial or “split” liver
- Living related donor segment
- Hepatocytes
  - Gene therapy
  - Donated

Orthotopic liver transplant

"The gold standard"

- Advantage:
  - Complete metabolic correction
- Disadvantages:
  - Requires a similar sized donor – very scarce resource
  - Immunosuppression required after
  - Some size limitations: tiny connections for tiny person

Consequence: scarce so requires triage to the most severe cases with the best neurologic outcomes with treatment

Partial or split liver

- Much more available
- Size matching still an issue, so may not be available for very small patients
- Still requires immunosuppression
- Yields metabolic correction or replacement of damaged organ

Living related donor

- Less chance for rejection
- Donor is readily available so can do as a planned procedure
- Size limitations – size of donor lobe and recipient liver site prevents its use in infants

Gene therapy

- Auto-transplantation with patient's own treated hepatocytes
- Advantage: no immunosuppression
- Disadvantages:
  - Invasive to patient to obtain hepatocytes
  - Vector safety

Donor Hepatocytes

- Advantages:
  - Readily available
  - No gene therapy vector required, cells have normal metabolism
- Disadvantages:
  - May need immunosuppression
  - Partial correction

Why even consider partial correction?

- Examples:
  - PKU and hyperphenylalaninemia
  - Forms of maple syrup urine disease
  - Urea cycle disorders spectrum of disease

Current trial with Cytonet

- Limited to infants with severe, neonatal onset urea cycle disorders
- Hepatocyte infusion as a bridge to transplant
- Requests examination of explanted liver at the time of transplant
- Goal is to stabilize or moderate severity of the disorders

Conclusions

- Liver transplantations may be lifesaving and is the therapy of choice for selected severe inborn errors of metabolism
- Livers are scarce
- Other options may provide stabilization or support pending transplant