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TWU T. Boone Pickens Institutes of Health Sciences
Houston J. and Florence A. Boswell
School of Nursing

Tyrosinemia Type I: A Case Study: The Value of Newborn Screening

Maria C. Reyes, MS, APRN, FNP-C , Barbara Gray, PhD, RN, CPNP

ABSTRACT

This case study presents a 12- year-old Hispanic male who presented to the pediatric primary care provider (PCP) for a health maintenance exam. His past medical history was significant for urgent liver transplantation at 20 months of age due to hereditary Tyrosinemia type I. This is a genetic disorder characterized by elevated blood levels of the amino acid tyrosine; if undiagnosed and untreated, the disorder can cause severe liver damage. The state of Texas expanded the mandatory newborn screening panel in 2007 to include amino acid disorders.

Over the last decade, outcomes of liver transplantation (LT) and survival rates have greatly improved. Patients with a history of LT once seen in liver centers are now followed in primary health care clinics. It is important for PCPs to be familiar with the overall care of patients who have a history of LT.

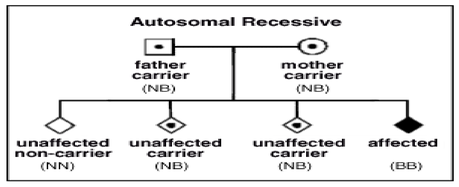
BACKGROUND TYROSINEMIA TYPE I

- Autosomal recessive genetic disorder
- Occurs in about 1 person in 100,000 worldwide, more common in Quebec, Canada (National Institutes of Health [NIH], 2008).
- Tyrosinemia type I is the most severe form of the disorder
- Caused by shortage of one of the enzymes required for the multistep process that breaks down tyrosine
- Deficiency of fumarylacetoacetase (FAH), (Online Mendelian Inheritance of Man [OMIM], n.d.)
- If untreated can result in possible liver failure – is potentially lethal disease (Couce et al., 2010; NIH, 2008)
- Clinical course characterized by acute liver failure in infancy or chronic liver dysfunction and renal Fanconi syndrome in cases that present at a later age (Nobili et al., 2010).
- Symptoms usually present in the first few months of life
- About 10% of newborns have temporarily elevated levels of tyrosine - probably due to vitamin C deficiency or immature liver enzymes (NIH, 2008)

TREATMENT

- No cure for tyrosinemia type I
- Special low protein diet required for lifetime that restricts tyrosine and phenylalanine
- May also be treated with nitisinone, which prevents the body from breaking down tyrosine.
- Special diet and nitisinone has greatly improved the outcome
- Early diagnosis and prompt treatment are essential
- Cases have been documented in which liver failure occurs regardless of therapeutic management and the special diet

GENETICS



Location of FAH Gene

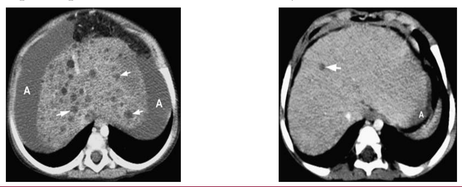
Cytogenetic Location: 15q23-q25
Molecular Location on chromosome 15: base pairs 80,445,232 to 80,478,923
The FAH gene is located on the long (q) arm of chromosome 15 between positions 23 and 25.
More precisely, the FAH gene is located from base pair 80,445,232 to base pair 80,478,923 on chromosome 15.

The Tyrosine Catabolic Pathway

BACKGROUND: LIVER TRANSPLANTS

- Approximately 5,000–6,000 liver transplantations (LT) performed each year (Aqel, 2009).
- Outcomes of LT improved significantly over the past 2 decades (Aqel, 2009)
- Recipients are now experiencing complications associated with longevity (Aqel ,2009)
- Rate of LT for children with hereditary tyrosinemia type I decreased over the last decade
- Early diagnosis with expanded NBS and treatment with Nitisinone (NTBC) (2-[2-nitro-4- trifluoromethylbenzyl]-1, 3-cyclohexanedione) is essential for an improved prognosis
- In some cases, liver failure occurs regardless of therapeutic management and special low-protein diet as a result of malnutrition from the low-protein diet (Shteyer, Simanovsky, Koplewitz, & Korman, 2011)
- Some individuals require LT if their liver disease is advanced before treatment begins (NIH [GARD], 2010)

Multiple Hepatic Lesions in a Girl with Tyrosinemia (Shteyer, et al., 2011)



NEWBORN SCREENING

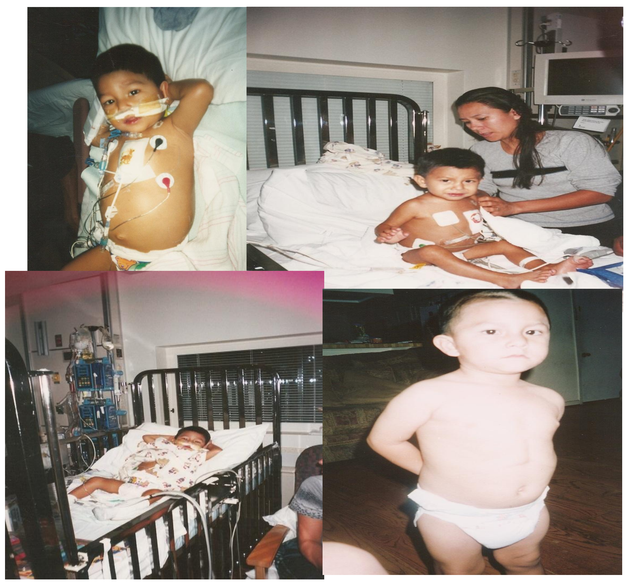
- In 2007, the Texas New Born Screening (NBS) program was expanded to test neonates for 28 rare disorders, including amino acid hereditary disorders
- A disorder identified early can prevent serious problems, such as intellectual disability, illness or death
- NBS did not screen for tyrosinemia type 1 in 1999, the year this patient was born
- This led to a delayed diagnosis of tyrosinemia and eventually a LT was required

FAMILY HISTORY

- Mother: healthy 34-year-old born in Mexico
- Father: healthy 36-year-old born in Mexico
- Paternal great grandmother, paternal grandmother, and paternal great-aunt: history of adult-onset DM
- Both maternal and paternal great-aunts: history of cancer of unspecified source

PERSONAL /SOCIAL/ MEDICAL HISTORY

- Lives in Houston with biological parents, 7-year-old brother, and 14-year-old half-sister
- 12-year-old Hispanic male
- DOB: October 18, 1999
- Currently in the 6th grade
- Urgent liver transplant on August 24, 2001
- Secondary to severe liver complications related to complications of tyrosinemia type I at age 20 months



EVIDENCE-BASED MANAGEMENT FOR TRANSPLANT PATIENTS

- Prograf (tacrolimus), a calcineurin inhibitor (CNI), used for patients after LT
- CNIs have numerous potential drug interactions
- Antifungals and antibiotics may increase the serum levels of CNIs resulting in a risk of toxicity
- Anticonvulsants, rifampin, orlistat, or St. John's wort may decrease the serum levels of CNIs resulting in the risk of organ rejection
- Prograf can lead to increased serum potassium levels
- Live virus vaccines contraindicated

CONCLUSIONS

- Outcomes and survival rates for LT recipients have been improving; patients are developing chronic conditions and seeking care from PCPs (McGuire et al., 2009)
- LT recipients are experiencing an increased prevalence of metabolic complications requiring collaboration between hepatologists and PCPs (Aqel, 2009)
- Coordination and communication between transplant hepatologists and PCPs is essential in order to prevent complications (Aqel 2009)
- PCPs can provide routine health care, including health maintenance exams and episodic visits. They should be familiar with the overall care of patients who have had liver transplants (McGuire et al., 2009)
- PCPs should be aware of the patient's medication regimen and adverse interactions with prescribed medications
- Opportunities are present for PCPs to collaborate with interdisciplinary teams