Overview of Galactosemia

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Galactosemia

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Case Presentation

- 3 d.o. sent to NICU for anuric, bleeding
- DOR 8 noted bloody stools, poor feeding
- At bedside ER lethargy, hypoglycemia noted
- History:
  - Preg, labor, delivery unremarkable
  - Full Term, BW 2.0 kg, home DOR 6 on Sialaduc
  - FIL unremarkable-2 healthy sibs
  - Still born in Illinois

Diagnosis

- Dx: Galactosemia (Gal-1-P uridyl transferase def.)
- GALT or GPUT deficiency
- All disorder of carbohydrate metabolism
- Presents with vomiting, diarrhea, lethargy, FTT, liver disease, jaundice common. 10% die within 10 days.
- Catarracts with few days of birth. RTA.
- Labs:
  - Red substance in urine, GAL-T in red cells (granulocytes), newborn screen
  - RX: Eliminate galactose (lactose) from the diet

Outline

- Signs/sympoms/impl timology
- Diagnosis
- Newborn screening
- Treatment
- Controversies
- Future

What is Galactosemia?

- Inherited metabolic disease/inborn error of metabolism
- Single enzyme defect
- Problem in metabolizing galactose sugar
- Galactose and glucose need to be interconverted for energy for the body
- This conversion is abnormal in galactosemia
Galactose Metabolism

History
- Individuals with galactose intolerance described as early as 1908 (see Itano, 1908)
- First American report was 1937 (Hansel and Turner Ann Pediatr Child 50:99, 1937)
- Schwartz et al suggested site of enzyme defects, found RSCs accumulated Gl-1-P (Schroeder 64:84, 1959)
- GALT deficiency
- Metabolic pathway for galactose worked out 1949, and 1953, major contributor was Lelard and pathway named after him, the Lelard pathway

Signs/symptoms/complications
- Typically, undiagnosed child will get sick at about day 5-9 of life, but usually presents in first weeks or 1st day of symptoms
- Poor feeding/ataxia, vomiting, jaundice, lethargy
- Often develop life-threatening bacterial infection, most commonly E. coli
- Liver disease common, can have liver failure
- Bleeding disorder related to liver disease

History (2)
- Segal and collagagues (ref. 1963, 1967) studied galactose metabolism in pts. with GALT deficiency
- Measured conversion of intravenous [14C] galactose to 14CO2
- Classic galactosemic pts. oxidized very little galactose
- No alternative pathways for galactose oxidation were identified

Signs/symptoms/complications (2)
- Usually evident very early
- Viral/upper respiratory infection
- Mental retardation if untreated
- Poor feeding/vomiting/growth failure/developmental delay/chronic liver disease
- Most untreated children die
- Most reversible if treatment begun quickly
Long term complications

- Only in recent years have we come to appreciate persistent complications in treated galactosemia.
- Speech/learning difficulties
- Behavior
- Ovarian failure
- Ataxia, tremor
- MRI abnormalities
- Osteopenia (Charbon PX, Pediatr 123:561, 1984)
- Growth may be delayed, but usually catch up

Long term complications (2)

- Present despite optimal treatment
- Age at start of diet (<2 mo), prenatal milk restriction, & Gal-1-4-P levels do not correlate with neuro psych development
  Wiegand, DD, Heart 13:106, 1962
  Schonfeld S, Ear Quad 10:26, 1975
  Charron MA, INDO 18:151, 1975
- Mean IQ 70-90, but above average intelligence in 10-20%

Ovarian failure

- >50% of women
- Delayed puberty
- Primary amenorrhea
- Secondary amenorrhea
- Oligomenorrhea
- Most have high FSH, LH levels
- Estradiol may be OL, with high FSH/LH, but then fall as ovarian failure progresses
- Don’t assume infertility

Speech and language deficits in early-treated children with galactosemia


- 8 children, 3.6-11 yr olds studied.
- Expressive language deficits in 7 of 8, with immediate recall and word retrieval skills notably affected.
- Articulation defects present in 5 of 8.
- Receptive language intact.
- Delayed vocabulary and articulation problems in > 90% children with galactosemia

Speech and language deficits galactosemia (cont.)

Hooper TW, Arch Pediatr 105:1217, 1996

- Unscreened group tested for speech, language

Verbal dyspraxia in treated galactosemia


- A specific pattern of speech/language difficulties in galactosemia was described
- 24 patients studied
- 54% had verbal dyspraxia
- Deficits in expressive vocabulary, grammar, and transposition of words within a phrase common
Diagnosis

- Confirmatory diagnostic testing done when NBS可疑，or with clinical suspicion
- Blood tests
  - GALc activity, GALc electrophoresis, G-1-P
  - Mutation analysis
- Whole body galactose oxidation
- Subsequent child in family with a child with galactosemia — cord blood GALc or mutation

Diagnosis (2)

- Urine tests
  - Reducing substances (e.g. Clinitest, different from ketosis i.e. suggestive but non-diagnostic)
  - Urine galactitol

Prenatal diagnosis

- Possible, if parents already have affected child
- Rarely requested

Preventing early death from galactosemia

- Symptoms too early, too non-specific for easy diagnosis
- Little to differentiate it from infection, etc
- Rare
  - DIFFICULT FOR HEALTH CARE PROVIDERS TO MAKE DIAGNOSIS IN TIME TO SAVE THE BABY

History of Newborn Screening

- Dr. Robert Guthrie - Arrowhead research in Buffalo, child with MR
- Active in state association for the mentally retarded
- Learned about PKU (phenylketonuria) — that if Rx’d, could prevent MR
- Guthrie had been working on bacterial inhibition assays (BIA) to detect antimetabolites in cancer patients
- Adapted to detect Phe
History (cont.)

- Niece of Dr. Guthrie's subsequently Dy'd with PKU at 35 mos.
- Developmentally delayed, autistic
- Too late to prevent MR
- Guthrie became interested in screening newborns for PKU
- Soon realized he could use the HEAs after collecting whole blood from newborns, pricking the heel, blotting drops of blood onto filter paper.
Filter paper technique was his greatest and lasting contribution.

Newborn Screening

- A filter paper test (Beutler test) for galactosaemia was developed in 1966 (Beutler E Edu Clin Med 80:37, 1966).
- Anil Beutler must be F/U by confirmatory tests because of false positives.
- Hill tests looks at galactose + gal-1-P

Newborn Screening (cont.)

<table>
<thead>
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<th>Phenylketonuria</th>
<th>Leucine</th>
<th>Cystinuria</th>
<th>Metabolites</th>
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<td>Tryptophan</td>
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Newborn Screening (cont.)

- Beutler test; beware heat inactivation, transfusion, G6PD deficiency
- Hill test; beware non-lactose diet
- Both; beware carriers, variants (DVG), early test
- Other tests
U.S. Newborn Screening

- 51 states have programs (includes D.C.)
- U.S. Military
- 4.5 million births annually
- 83 hemoglobin (c. 1995)
- Lack of uniformity in testing—worse than ever
- HRSA/ACMG looking at standardization
- Only 50 of 51 screen for galactosemia
- Screening not universal in Europe (e.g., 95%)

Newborn screening in the U.S. saves > 3,600 infants per year from death or mental retardation
(prior to advent of expanded newborn screening)

Tandem Mass Spectrometry (MS/MS)

Blood spot & Metabolites → MS1 → MS2

Galactosemia Variants

- Segal et al. (1968, 1969) studied galactose metabolism in pts. with GALT deficiency
- Measured conversion of radioactive [14C]galactose to PCP
- Most pts. showed very little galactose
- Galactosemia pts. excreted galactose at normal rates even though GALT deficient in RBC's
- This subset of pts. were all Black
- Galactosemia in Blacks was noted to often be milder
- Hypogenital variant of galactosemia with altered pathway for galactose or differential expression of enzyme variants

Galactosemia variants (cont.)

- Black variant
- Duarte (DG)
- Los Angeles
- Galactokinase
- Epimerase
- False positive newborn screening test—G6PD, heat, liver disease, liver shunt
Treatment

- Infants suspected of having galactosemia should have all lactose-containing feedings discontinued immediately.
- Breastfeeding and cow milk formula must be stopped.
- Calcium-enriched soy milk (soy formula ok only through infancy) and/or calcium supplementation.

- Dietary
  - Galactose restriction
  - Must galactose in lactate, dairy products
  - Lactose in milk, sugar, galactose-phosphate
  - Easy in infants, use soy formula
  - More difficult in older children, need to read food labels, etc.
  - School assistance, CT/FP/Speech, early intervention
  - Treat delayed puberty in girls

Monitoring

- Blood Gal-1-P
  - Goal: Depends on lab & urine—generally 150 mmol/L, 50 mg/dl PBC, normal RBCs, <5 nmol/g Hgb
  - Urine galactosed
  - FTU in a Metabolic Clinic
  - Monitor development
  - Keep abreast of research, new treatments/complications
  - Network with other physicians caring for children with galactosemia—research and clinics

Monitoring (2)

- FTU in a Metabolic Clinic (cont.)
  - Dietary consultation with a metabolic dietitian for assessment and advice
  - Recognize late complications
  - Usual health care, Metabolic Clinic visits do not replace
  - Regular ophthalmologic exams

Monitoring (3)

- Up to age 1 yr: Q 3 mo visits to specialist team
- 1-2 years: Q 4 mo
- 2-14 years: Q 4 mo
- Annually thereafter
- More frequent for girls in late childhood and adolescence
- Specialist speech assessments 1 and 2 years
- Specialist developmental at 4, Kj at 8, 14, 18 years

Monitoring (4)

- Walter stipulates management of FSH, LH, estradiol at 6 mos, 10 and 12 yrs, yearly thereafter, refer to endocrine by 10 yrs
- May need hormone Rx
- Around 12-16 years—hormone treatment should contain lactose but usually small amount

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Genetics

- Autosomal recessive genetic condition
- Recurrence risk 1 in 4 (25%)
- Incidence about 1 in 20,000 births
- Gene defect identified, mutations in the GALT gene identified

Molecular Genetics of GALT

- Full length cDNA for GALT gene cloned back to lab by 1989
- Sequenced by Fluck, Reinerth, and Hinz (1996)
- 13.4 kb cDNA codes for 44 kDa protein with 379 AA
- Gene has 11 exons, 10 introns spanning 4 kb
- Active site in exon 5, positions 184-185
- Several different mutations found in galactosemia
- Mutations heterogeneous, a few are common
- Some mutations appear to result in an unstable protein, others result in diminished enzyme activity

Mutations in GALT

- Q188R. A to G transition (galactose in ergobine)
  - 6/104 alleles, prevalence 46% by 1 study
  - Associated with severely reduced enzyme activity
  - Studies attempting to correlate genotype with phenotype by Dr. Han & others suggest Q188R in general associated with more severe form
  - Recently a mutation (G133L) C to T transition at base pair 1338, Serrat to Leucine previously thought to be a neutral mutation (polymorphism) found in Black galactosemic (Kieser, 1994, Lack and Issener, 1994)

Mutations in GALT (Cont)

- Duarte variant galactosemia: N314D
- Careful, can sometimes be >1 mutation on same allele

Controversies

- Restrict galactose in certain fruits, etc
  - Galactose present in many fruits and vegetables, and in glycosidic linkages in other plant and animal products, but no evidence galactose from these sources make a significant contribution to the dietary galactose load
  - Larger quantity in some legumes such as peas and lentils
  - Medications-galactose content

Controversies (2)

- Soy formula may have too much galactose
  - Elemental formulae (Neocate, Alcaren)?
  - Prenatal treatment
  - When can restriction be relaxed?
    - Diet for life
    - Newborn screening—WA State, United Kingdom

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Controversies (3)

- Endogenous galactose production (Review)
- What about gal causes the complications?
- Why are some women able to have children
  without assistive reproductive technology?

Future

- Studies of pathology, Rx in animal model
- Elemental formulas to eliminate all
  galactose intake in young infants
- Gene therapy
- Enzyme replacement therapy
- Stem cell therapy