Overview of Galactosemia

Robert D. Steiner, M.D.
Oregon Health & Science University

Galactosemia

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Oregon Health & Science University

Outline

- Case presentation
- History
- Biochemical basis
- Genetic basis
- Variants: Black, DG
- Signs/symptoms/complications
- Diagnosis
- Newborn screening
- Treatment
- Controversies
- Future

Case Presentation

- 7 d.o. sent to NICU for acidosis, bleeding
- DOL 6 noted bloody stools, poor feeding
- At outside ER-lethargy, hypoglycemia noted
- History
  - Preg, labor, delivery unremarkable
  - Full Term, BW 2.9 kg., home DOL 4 on Similac
  - FH unremarkable--2 healthy sibs
  - SH born in Illinois

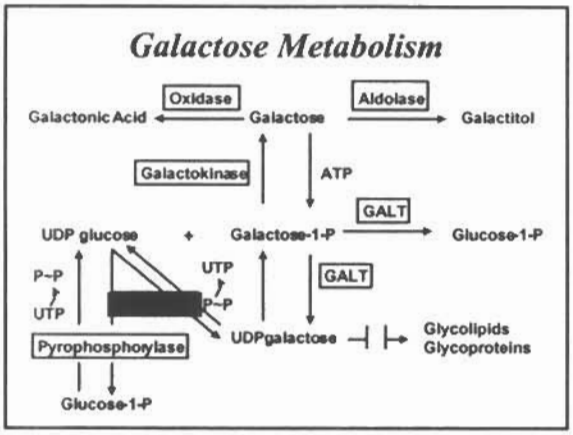
- PE: Pt. In shock. Wt, length, OFC 10th%, lungs clear with tachypnea, cardiac-RRR without murmer, abdomen-liver down 2cm., neuro-lethargic, hypotonic, DTR's intact
- Labs: ABG 7.2/14/95, Na 149, K 3.8, Co2 8, Hgb 15, PT,PTT >100, NH3 106, lactate 9.6M, glu 75, plt 96K, LP 0 WBC's, Bili 20/4, SGOT 87, SGPT 255
  - SAA increased tyr, met, phe; UOA 4+ p-OH-phenylacetate, 3+lactate, urine reducing substances +, Ketostix: - blood, - protein, - sugar
  - Blood culture--E.Coli
- Course
  - Intubated, fluid resuscitated, ABX, FFP, improved over 24 hrs, went home with no sequelae

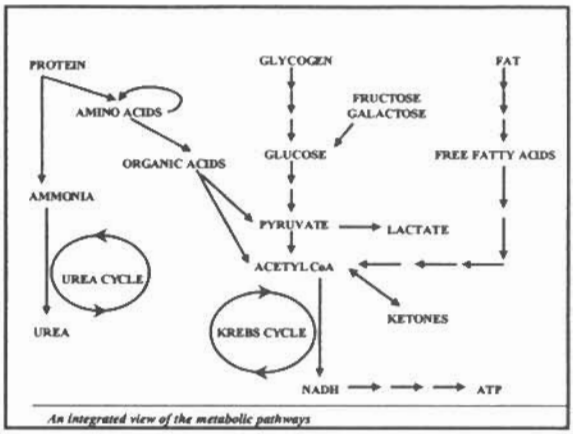
Diagnosis

- Dx: Galactosemia (Gal-1-P uridyl transferase def.)
- GALT or GPUT deficiency
- AR disorder of carbohydrate metabolism
- Presents with vomiting, diarrhea, lethargy. FTT, liver disease, jaundice common. E.coli sepsis!! Cataracts w/i few days of birth. RTA.
- Labs
  - Red substances in urine, GALT in red cells (transfusion), newborn screen
- RX: Eliminate galactose (lactose) from the diet

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





History

- Individuals with galactose intolerance described as early as 1908 (von Reuss, 1908)
- First American report was 1917 (Mason and Turner Am J Dis Child 50:359, 1935)
- Schwarz et al suggested site of enzyme defect, found RBCs accumulated G-1-P (Biochem J 62:34, 1956)
- Conf by Isselbacher (Science 123:635, 1956)
- Metabolic pathway for galactose worked out 1949, and 1953, major contributor was LeLoir and pathway named after him, the Leloir pathway (Caputto R, et al, JBC, 184:333, 1950, Leloir LF. Arch Biochemm 33:186, 1951)

History (2)

- Segal and colleagues (1965, 1966, 1968) studied galactose metabolism in pts. with GALT deficiency
- Measured conversion of intravenous [^{14}C] galactose to $^{14}CO_2$
- Classic galatosemic pts. oxidized very little galactose
- No alternative pathways for galactose oxidation were identified

Signs/symptoms/complications

- Typically, unidentified child will get sick at about day 5-9 of life, but usually presents in first weeks as life threatening illness
- Poor feeding/wt loss, V/D, 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

Signs/symptoms/complications (2)

- Cataracts evident very early
- Vitreous hemorrhage
- Mental retardation if untreated
- Poor feeding/vomiting/growth failure/developmental delay/chronic liver disease if undetected/untreated and children don't become acutely ill
- 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 galactosemics.**
- Speech/learning difficulties
- Behavior
- Ovarian failure
- Ataxia, tremor
- MRI abnormalities
- Osteopenia (Kaufman FR J Pediatr 123:365, 1993)
- Growth may be delayed, but usually catch up

Long term complications (2)

- Present despite optimal treatment
- Age at start of diet (<2 mos), prenatal milk restriction, & Gal-1-P levels do not correlate with neuropsych development
  Waggoner, DD JIMD, 13:802, 1990; Schweitzer S: Eur J Ped 152:36, 1993; Cleary MA: JIMD 18:151, 1995
- Mean IQ 70-90, but above average intelligence in some

Ovarian failure

- >90% of women
- Delayed puberty
- Primary amenorrhea
- Secondary amenorrhea
- Oligomenorrhea
- Most have high FSH, LH levels
- Estradiol may be nl, 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

Waisbren SE, Norman TR, Schnell RR, Levy HL. J Pediatr 102:75, 1983

- **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 deficits present in 5 of 8. Receptive language intact.**
- **Delayed vocab and articulation problems in > 90% children with galactosemia**

Speech and language deficits galactosemia (cont.)

Hansen TW, Acta Paediatr 85:1197, 1996

- **Unscreened group tested for speech, language**

Verbal dyspraxia in treated galactosemia

Nelson CD, Waggoner DD, Donnell GN, Tuerck JM, Buist NRM. Pediatrics 88:346, 1991

- **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 abnl, or with clinical suspicion
- Blood tests
  - GALT activity, GALT electropheresis. G-1-P
  - Mutation analysis
- Whole body galactose oxidation
- Subsequent child in family with a child with galactosemia—cord blood GALT or mutation

Diagnosis (2)

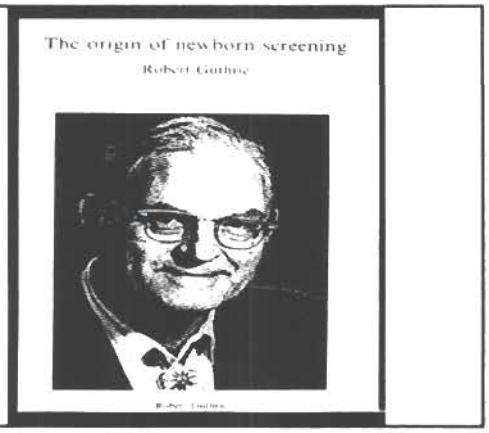
- Urine tests
  - Reducing substances (ie Clinitest, different from ketostix); suggestive but non-diagnostic
  - Urine galactitol

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

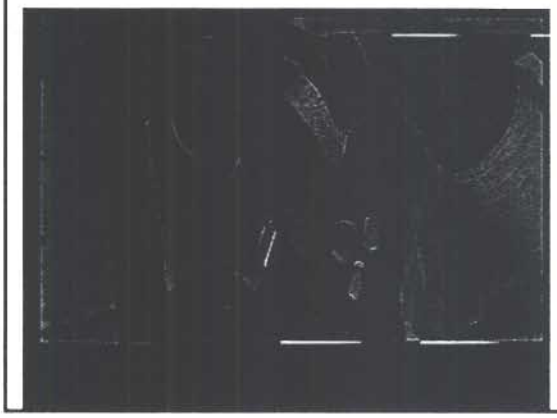


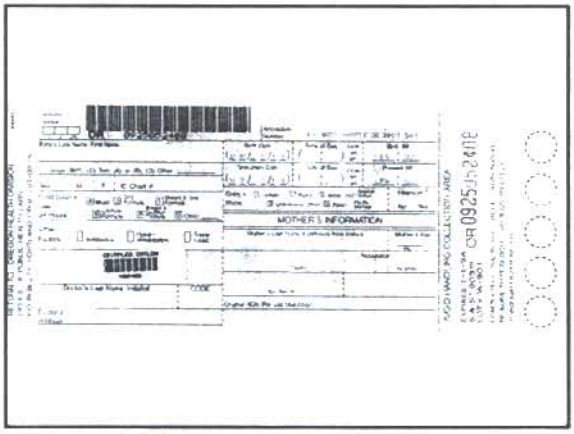
History of Newborn Screening

- Dr. Robert Guthrie--cancer researcher 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 Dx'd with PKU at 15 mos.
- Developmentally delayed, autistic
- Too late to prevent MR
- Guthrie became interested in screening newborns for PKU
- Soon realized he could use the BIAs 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 galactosemia was developed in 1966 (Beutler E J Lab Clin Med 68:137, 1966)
- Abnl Beutler must be F/U by confirmatory tests because of false positives
- Hill tests looks at galactose + gal-1-P

Newborn Screening (cont.)

Metabolites	
Phenylalanine	Tyrosine
Leucine	Methionine
Galactose (+Gal-1-PO_4)	
Enzymes	
Beutler (galactosemia)	Biotinidase
Trypsin?	Others?
Hormones	
T_4	17-OH Progesterone
TSH	Others?
Proteins	
Hemoglobin	Others?

Newborn Screening (cont.)

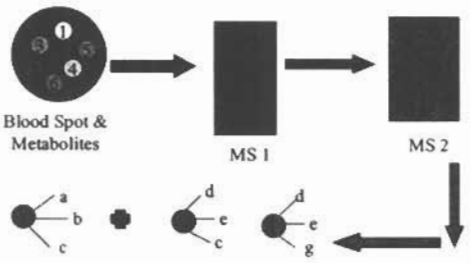
- **Beutler test: beware heat inactivation, transfusion, G6PD deficiency**
- **Hill test: beware non-lactose diet**
- **Both: beware carriers, variants (D/G), early test**
- **Other tests**

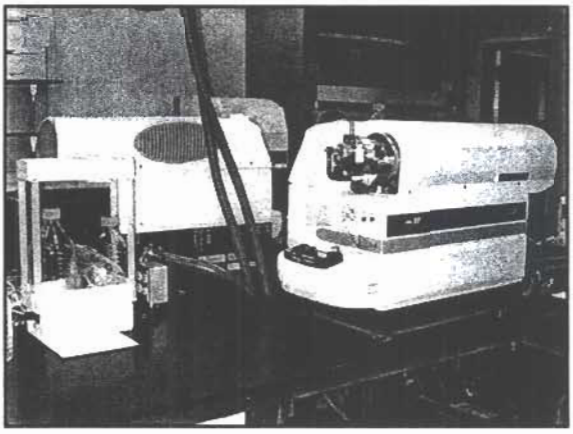
U.S. Newborn Screening

- 51 states have programs (includes D.C.)
- U.S. Military
- 4.3 million births annually
- 83 laboratories (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 (UK 9%)**

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)





Galactosemia Variants

- Segal et al (1965, 1966, 1968) studied galactose metabolism in pts. with GALT deficiency
- Measured conversion of intravenous [^{14}C]galactose to $^{14}CO_2$
- Most pts. oxidized very little galactose
- Subset of pts. oxidized galactose at near-nl rates even though GALT deficient in RBC's
- This subset of pts. were all Black
- Galactosemia in Blacks was noted to often be milder
- Hypothesized: variant of galactosemia with alternative pathway for galactose or differential expression of enzyme various tissues

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

Treatment

- Dietary
  - Galactose restriction
  - Most galactose in lactose, dairy products
  - Lactose is milk sugar, galactose-glucose
  - Easy in infants: use soy formulas
  - More difficult in older children, need to read food labels, etc
- School assistance, OT/PT/Speech, early intervention
- Treat delayed puberty in girls

Monitoring

- Blood Gal-1-P
  - Goal: Depends on lab & units--generally 150 umol/L, 50 ug/ml PRBC, 5mg/dl RBCs, 0.5 umol/g Hgb
- Urine galactitol
- F/U in a Metabolic Clinic
  - Monitor development
  - Keep abreast of research, new treatments/complications
  - Network with other physicians caring for children with galactosemia—research and clinical

Monitoring (2)

F/U 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)

- UK Galactosemia Steering Group (Walter JH Arch Dis Child 80:93, 1993)
- Up to age 1 yr: Q 3 mo visits to specialist team
- 1-2 years Q 4 mos
- 2-14 years Q 6 mos
- Annually therefater
- More frequent for girls in late childhood and adolescence
- Specialist speech assessments 1 and 2 years
- Specialist developmental at 4, IQ at 8, 14, 18 years

Monitoring (4)

- UK Galactosemia Steering Group (Walter JH Arch Dis Child 80:93, 1993)
- Walter suggests measurement of FSH, LH, estradiol at 6 mos, 10 and 12 yrs, yearly thereafter, refer to peds endocrine by 10 yrs
- May need hormone Rx
- Around 12-16 years--hormone treatments-- may contain lactose but usually small amounts

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 Reichardt and Berg (1988)
- Sequenced by Flach, Reichardt, and Elsas (1990)
- Entire gene cloned and sequenced by Leslie et al (1992)
- 1.3 kb cDNA codes for 44 kDa protein with 379 AA
- Gene has 11 exons, 10 introns spanning 4 kb
- Active site in exon 6, positions 184-186
- Several different mutations found in galactosemia
- Mutations heterogenous, though 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 (glutamine to arginine) 69/104 alleles, prevalence = 66% in 1 study
- Associated with severely reduced enzyme activity
- Studies attempting to correlate genotype with phenotype by Dr. Elsas & others suggest Q188R in general associated with more severe form
- Recently a mutation (S135L) (C to T transition at base pair 1158, Serine to Leucine) previously thought to be a neutral mutation (polymorphism) found in Black galactosemics (Elsas, 1996, Landt and Steiner, 1996)

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 gal from these sources make a significant contribution to the dietary galactose load
  - Larger quantities in some legumes such as peas and dried beans
- Medications-galactose content

Controversies (2)

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

Controversies (3)

- Endogenous galactose production (Berry GT/Segal S and colleagues: Lancet 346:1073, 1995)
- 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 (Leslie ND: Biochem Mol Med 59:7, 1996)
- Elemental formulas to eliminate all galactose intake in young infants
- Gene therapy
- Enzyme replacement therapy
- Stem cell therapy