Galactosemia

Dr Michel Tchan
Adult Genetic Metabolic Disorders Service
Westmead Hospital
Galactosemia

• People with galactosemia are unable to metabolize the simple sugar galactose.

  • infantile cataracts,
  • jaundice,
  • vomiting,
  • poor feeding,
  • infections
  • Failure to thrive,
  • hepatomegaly
  • Speech disabilities,
  • Sub-fertility
  • (Intellectual disability)

POTENTIALLY LETHAL IF UNDIAGNOSED/UNTREATED
Galactose in Health

- Galactose is a vital energy source, particularly for babies
- Mostly found in dairy products as part of a sugar “lactose”
- Important for putting sugars onto proteins (glycosylation)

- We make some galactose internally, about 1000 – 2100 mg daily (adults, higher in children).
History

• Galactosemia was first discovered in 1908 by the physician Von Ruess.

• Publication entitled, "Sugar Excretion in Infancy," reported on a breast-fed infant with failure to thrive, enlargement of the liver and spleen, and "galactosuria".

• 1935 Treatment described by Mason and Turner
• Now diagnosed by newborn screening in Australia
Galactose

- Six carbon aldose carbohydrate
- Major dietary source is lactose from milk and milk products
- Epimer of glucose
  - Differs from glucose at carbon 4
Galactose Metabolism

“The Leloir pathway”

Lactose \[\rightarrow\] β-D-Galactose \[\rightarrow\] Galactose mutarotase \[\rightarrow\] α-D-Galactose

\[\text{UDP-Gal:Gal-1-P uridylyltransferase}\]

\[\text{phosphoglucomutase}\]

\[\text{Glucose-1-phosphate}\]

\[\text{Glucose-6-phosphate}\]

Lactose: a sugar found in milk

In the body, lactose is cleaved to form glucose and galactose

Used for energy

Normal

Galactose concentration rises to toxic levels, causing:
- kidney failure
- enlarged liver
- cataracts
- brain damage

Galactosemia

No GALT. Galactose concentration rises to toxic levels, causing:
- kidney failure
- enlarged liver
- cataracts
- brain damage

copyright M.W. King 1997
Galactosemia – a genetic disease

• Galactosemia is an inherited disorder.

• Autosomal recessive pattern

- It occurs in approximately 1 out of every 60,000 births among Caucasians.
- About 6 or 7 babies a year
- The rate is different for other groups.
Four forms of galactosemia

- Galactose-1 phosphate uridyl transferase deficiency (classic galactosemia, the most common and most severe form) - (GALT) Type I

- Deficiency of galactose kinase – (GALK1) Type II

- Deficiency of galactose-6-phosphate epimerase (GALE) Type III

- Deficiency of galactose mutarotase – (GALM) Type IV
Classic galactosemia – GALT _ type I

- **Galactose-1-phosphate uridyltransferase defect** causes accumulation of **galactose**
- Galactose changes to **galactitol**. Galactitol accumulates in lens and causes **infantile cataracts**.
- Jaundice, vomiting, poor feeding, infections
- Failure to thrive, hepatomegaly
- Speech disabilities,
- Female sub-fertility
- (Intellectual disability)
• The official name of this gene is “galactose-1-phosphate uridylyltransferase.”

• GALT is the gene's official symbol.

• Cytogenetic Location: 9p13
Missense mutations within the GALT gene

**S135L** = Leu for Ser
- Almost exclusively in individuals of African decent
- 50% of African American mutations

**K285N** = Asn for Lys
- 2nd most common disease-causing mutation

**Q188R** = Arg for Gln
- Classic galactosemia
- 60-70% of mutated chromosomes

**N314D** = Asp for Asn
- Duarte and LA alleles
- 2 variations: D1 & D2
Q188R

- Most deleterious mutation on GALT gene
- Ireland and British (highest frequency)

- Homozygous individuals show no activity (*in vitro*)
Galactosemia clinical picture

- Infantile cataracts,
- jaundice,
- vomiting,
- poor feeding,
- infections
- Failure to thrive,
- hepatomegaly
- Speech disabilities,
- Female sub-fertility
- (Intellectual disability)
Cause of Symptoms?
Complex! Poorly understood

Galactose $\xrightarrow{\text{Aldose Reductase}}$ Galactitol

- Buildup of galactitol?
  - Intellectual disability
  - Cataracts
  - Ovarian damage

- Buildup of galactose-1-phosphate?
  - Liver and renal damage
  - Intellectual problems
Type 1 – what do we know clinically?

• Recently published comprehensive study (Rubio-Gozalbo et al 2019)
  • GalNet
  • 509 patients worldwide
  • Aged 0 to 65 years
  • 93% Caucasian in this study
  • Q188R was 57.7% (233/404)
  • Diagnosed on NBS in 45.9% (215/468)
Neonatal illness

• reported in 79.8% (332/416)
  • elevated liver enzymes in 70.3% (211/300),
  • bleeding diathesis in 42.5% (128/301),
  • encephalopathy in 29.0% (71/245),
  • clinical signs of infection in 27.4% (96/351),
  • cataract in 25.8% (68/264) and
  • hypoglycemia in 25.1% (65/259).

• Early detection and treatment saves lives
Neurological, cognitive and behavioral complications

A

- Developmental delay infancy/childhood: 18/167
- Motor developmental delay: 68/167
- Cognitive developmental delay: 33/167
- Motor and cognitive developmental delay: 128/164
- Language delay: 37/170

B

- Language and speech disorders: 192/289
- Speech defect: 129/315
- Impairment in vocabulary: 117/288
- Impairment in grammar: 96/253
- Verbal dyspraxia: 67/255
- Dysarthria: 48/246

C

- Neurological complications: 104/336
  - Tremor: 104/336
- General motor abnormality: 85/319
  - Ataxia: 40/329
- Seizures: 25/220
- Dystonia: 24/118

D

- Mental and behavioral problems: 126/288
  - Anxiety disorder: 67/300
- Depression: 36/303
- ADHD: 21/286
- Autism spectrum disorder: 17/281

* Defined as having at least one of the complications in that category, compared to having none of them.
* Language delay and motor and/or cognitive developmental delay.

Frequency of neurological, cognitive and mental (psychiatric) complications. 

- A Developmental delay infancy/childhood.
- B Language and speech disorders.
- C Neurological complications.
- D Mental (psychiatric) and behavioral problems. The n/valid n is shown per outcome.
Sub-fertility

- Premature ovarian insufficiency (POI) was reported in 79.7% (118/148) of female patients.
- In females aged > 35 years, POI percentage increased to 85.1% (40/47)
- 16.8% (16/95) of female patients with POI tried to conceive and 25.0% (4/16) of these women successfully became pregnant without assisted reproduction.
- p.Gln188Arg mutation was associated with a higher odds ratio for POI
- 7.8% (5/64) males had fathered a child
Bone health

• Low bone density in 26.5% (76/287) of the patients, where 65.8% (50/76) were female

• The majority of patients received calcium and vitamin D supplements (68.2% (281/412) and 71.1% (288/405), respectively)
Cataract

- Cataract in the neonatal period in 25.8% (68/264).
- In 54.5% (24/44) the cataract disappeared after introduction of diet, whereas in 45.5% (20/44) of patients a residual cataract was documented.
- A minority of patients developed cataract after the neonatal period, 9.2% (22/238).
- There was another group of patients, 11.2% (10/89), in whom cataract was reported in adulthood (median 29.5 years, range 18 to 41 years)
Diet

• After the neonatal period, most of the patients followed a lactose-free diet, 94.2% (406/431).

• relaxed diet (lactose free without further restrictions), in 64.3% (245/381)

• strict diet (lactose free and restriction of non-dairy sources) in 35.7% (136/381)
Genetic variations - GALT

- The **Duarte (D2) variant** is found in 1 in 20 persons.
- May be detected on NBS
- GALT enzyme (10-25% to 50% activity) and do not have any symptoms.
  - Do not develop illness in the newborn period
  - 350 children ages six to 12 years reported no detectable differences in developmental outcomes
  - No reports of female sub-fertility

- Carlock et al 2019
Galactokinase – deficiency or galactosemia Type II

• First identified in 1965,
  • cataracts and galactosuria that developed upon drinking milk.

• Neither liver disease nor signs of mental impairment were present.

• No accumulation of galactose-1-phosphate despite the accumulated galactose.
• The official name of this gene is “galactokinase 1.”
• GALK1 is the gene's official symbol.
• Cytogenetic Location: 17q24
Clinical pictures of Galactosemia Type II

- Mild
- Cataract in the infant
Type II

• Quite rare
  • <60 patients reported

• Cataract if not on diet

• Low galactose diet is recommended

• Rare reports of pseudotumour cerebri
  • Fluid buildup around the brain

• No other health concerns reported

• A Bosch etal 2002 JIMD
Galactose epimerase (GALE) deficiency – galactosemia - Type III

• The official name of this enzyme is “UDP-galactose-4-epimerase.”

• More than 20 mutations in the GALE gene have been identified in people with a form of galactosemia known as type III or galactose epimerase deficiency.
UDP-galactose-4-epimerase deficiency

- Cytogenetic Location: 1p36-p35
- GALE is the gene’s official symbol
Epimerase deficiency

• Originally described as a benign condition in 1972 (Gitzelman) “peripheral”
• Then a patient was found to have symptoms like GALT galactosemia in 1981 (Holton)
• Finally, Openo in 2006 showed that patients are on a spectrum between these two extremes

• So some GALE patients need a restricted galactose diet, and some do not.
  • Diet cannot be completely restricted due to the place of the enzyme block
• Learning difficulties may occur
• Ovarian failure does NOT seem to occur
Galactose Mutarotase deficiency - GALM (Type IV)

- Chromosome 2p21
- GALM is the official gene name
- Only described this year by Dr Wada
Galactose Mutarotase deficiency - GALM (Type IV)

• increased blood galactose concentrations with no change in the levels of galactose 1-phosphate.
• None of the eight patients presented with gastrointestinal symptoms or severe liver dysfunction,
• Two patients presented with bilateral cataracts.
• No adult patients were examined
• All patients were treated with a galactose-restricted diet immediately after the diagnosis of galactosemia
• Two of these patients were allowed to resume a normal diet.
Galactosemia diet

• The diet should be low in lactose (dairy products)

• Babies
  • No breastfeeding
  • Formula for the first 4-6 months (Soy based or specialised eg Neocate)

Handbook for Galactosaemia

Australasian Society for Inborn Errors of Metabolism
Diet

• Avoid
  • Animal milks (Cows milk contains 2350mg of galactose per 100ml)
  • “Lactose free” dairy foods
  • Lactose in medicines (careful!)
  • Chickpeas (eg hummous, Besan flour)
  • Some fermented soy products
  • Offal

• Old “hard” cheeses are often OK
<table>
<thead>
<tr>
<th>Food Group</th>
<th>Allowed</th>
<th>Not Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk &amp; Milk Substitutes</td>
<td>Soy or MCT Formula: Neocate</td>
<td>Breast Milk, Animal Milk, Cheeses, Butter, Ice Cream, Yogurt</td>
</tr>
<tr>
<td>Fruits</td>
<td>Most Frozen, Fresh, Canned &amp; Dried*</td>
<td>Dates, Papaya, Persimmon, Watermelon</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Most Frozen, Fresh, Canned, &amp; Dried*</td>
<td>Bell Peppers, Tomatoes</td>
</tr>
<tr>
<td>Meats &amp; Meat Substitutes</td>
<td>Beef, Poultry, Lamb, Ham Pork, Fish, Game, Kosher Franks, Eggs, Nuts</td>
<td>None*</td>
</tr>
<tr>
<td>Breads</td>
<td>Rice, Pasta, Cereals, Breads</td>
<td>None*</td>
</tr>
<tr>
<td>Fats</td>
<td>Oil, Lard, Shortening, Mayonnaise</td>
<td>Butter, some margarines</td>
</tr>
</tbody>
</table>
Thank you!