Galactosaemia an update

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Abstract

While galactosaemia was originally documented over 100 hundred years ago, it still remains poorly understood and recognized. Classical galactosaemia is an inherited disorder of galactose metabolism, whose main dietary source is lactose. In the UK which does not currently screen for galactosaemia lack of recognition of key symptoms can lead to delays in diagnosis. However it has become clearer that Galactosaemia is not only an acute disease of the neonatal period but affected children potential are prone to a number of chronic problems later in life. This review looks at the current thinking concerning the pathogenesis and complications of galactosaemia and summaries our current management of patients.

Keywords galactitol; galactosaemia; galactose-1-phosphate; genetic; inherited metabolic disease; leloir pathway

Definition

The pathogenic potential of ingested galactose was originally described over 100 years ago. It results from a defect in the galactose metabolic pathway, the Leloir pathway, which consists of three enzymes, the galactose specific kinase (Galactokinase/GALK), galactose-1-Phosphate uridyltransferase (GALT) and uridine diphosphate galactose 4’ epimerase (GALE). While a deficiency in any of these enzymes will lead to the biochemical finding of galactosaemia i.e. an elevated plasma galactose, only deficiencies in GALT or GALE have the potential to cause the ‘classical Galactosaemia’ phenotype: an acute toxicity syndrome which resolves on removal of exogenous galactose intake with more recently recognized long-term complications of chronic neurological, endocrine, and orthopaedic problems. The outcome of these chronic problems seems to be far less tightly linked to galactose intake.

Incidence/epidemiology

The overall incidence of classical galactosaemia, secondary to GALT deficiency, is estimated at between 1: 23,500 and 1: 44,000 in the UK. This is in keeping with most of Western Europe, however the incidence in different subpopulations varies greatly. This is especially true in Ireland, where the incidence in the travelling population is one in 450 live births whilst the overall incidence is nearer to 1: 20,000. Worldwide the incidence does appear to be lower than in Western Europe, being quoted as one in 50,000 in the USA and as little as one in 100,000 in Japan.

The mild asymptomatic phenotype of GALE is relatively common, with a frequency of 1: 6,200 in the African American population, but the severe “generalized” presentation of GALE, whose presentation is similar to that of classical galactosaemia is limited to a few case studies worldwide. The GALK deficiency is rare <1/100,000.

Genetics

The GALT gene is located on chromosome 9p13 and consists of 11 exons. Over 230 mutations have been described. The most frequent mutation in the Caucasian population, with an overall frequency of 65% (96% in the Irish population), is the Q188R mutation, which results in a complete loss of enzymic activity. The second commonest European mutation is the K285N, a missense mutation, which predominates in central European counties. This also results in a complete lack of GALT activity. In contrast, S135L, which accounts for 50% of mutate alleles in African Americans, shows near normal activity in mouse models. Whilst there is a relatively good correlation between genotype and residual enzymic function, the correlation between genotype and clinical phenotype is more enigmatic, though Q188R is predictive of a poorer clinical outcome, whereas S135L is associated with the milder phenotype seen in Afro-Caribbean patients.

The N314D mutation (c. 940A>G), so called Duarte variant, can exist in two different forms: Duarte-1 and Duarte-2 has a good clinical outcome. The Duarte-2 mutation is interesting, as compound heterozygotes for the Duarte-2 variant and classical galactosaemia, typically manifest 14–25% of normal GALT activity resulting in some protection against severe toxicity.

Pathology

The exact mechanisms underlying the pathophysiology of classical galactosaemia is still not fully understood with the lack of a good animal model hampering research; the GALT mouse knockouts, having few of the clinical features found in humans. However, the potential mechanisms can be grouped into, primary effects which include the buildup of toxic metabolites and the reduction in end products of the Leloir pathway and secondary effects due to disruption of other interlinked pathways.

With any disruption of the Leloir pathway, there is the potential for excess galactose accumulation, which if uncontrolled will also result in accumulation of Galactitol and Galactonate. These are formed due to the actions of the alternative pathways of galactose metabolism i.e. aldase reductase and the pentose phosphate pathway respectively (Figure 1).

Given that the GALK deficient patients do not manifest either the acute toxicity, or any of the chronic manifestations seen in GALT patients, it seems likely that Galactose-1-P which is absent in GALK but present in GALT, plays a major role in their
pathogenesis. The actions of GAL-1-P need further elucidation with a variety of effects being seen, for a more comprehensive review see Lia 2009. Recently there has been some speculation that GAL-1-P toxic effects may be mediated via the human tumour suppressor gene alysia ras homolog I (ARHI), which, since it is absent in mice, may also explain the clinical difference seen in the mouse model. The accumulation of galactitol is thought to be responsible for the cataracts seen, though whether this is due to direct osmotic effects or due to oxidative damage secondary to NADPH depletion is unclear. It is also unclear if galactonate, cleared by the pentose 5 phosphate pathway, contributes to the overall toxicity.

In terms of reduction of end product, the interplay of the enzymes involved in the Leloir pathway ultimately controls the levels of UDP-galactose, the galactosyl donor in cellular glyco-protein/glycolipid biosynthesis. This potentially leads to abnormalities in post translational protein modification and abnormal glycosylation has been demonstrated with abnormalities seen in FSH and transferrin changes similar to those seen in congenital disorders of glycosylation (CDG).

The most apparent affect on a secondary pathway, is the reduction in levels of cellular inositol, with reductions in myo-inositol being documented in vivo. GAL-1P competitively inhibits human inositol monophosphatase and in the yeast model, galactose toxicity can be overcome by over-expression of inositol monophosphatase. The reduction in inositol might partially explain the neurological symptoms seen in galactosaeic patients since inositol is required for the formation of the neuronal modulator Phosphatidylinositol bisphosphate.

**The clinical symptoms of acute toxicity syndrome of classical galactosaemia**

The natural history of classical galactosaemia is of an early onset, potentially life threatening acute toxicity syndrome, occurring after several days of exposure to dietary galactose from milk. However liver dysfunction has been described as early as day 1 and milder phenotypes presenting at several weeks of age are seen. Overall, in 266 out of 336 cases (79%) in one study, acute symptoms were reported within 2 months of birth.

Initial symptoms are non specific with affected neonates presenting with vomiting, diarrhoea, lethargy, hypotonia or poor feeding with resultant poor weight gain. Given the limited neonatal repertoire of response to illness, this is easily confused with sepsis, a situation complicated further by the apparent susceptibility of galactosaeics to *Escherichia coli* sepsis.

Examination on presentation may reveal signs of liver impairment such as jaundice, hepatomegaly and signs of abnormal bleeding; as well as occasional fullness of the anterior fontanelle either due to sepsis or pseudotumour cereberi. While cataracts are a recognized feature of GALT deficiency they are infrequent with only 14% of patients affected in one series with only 20% of these presenting in the neonate period. Even when present, they may require the use of a slit lamp for visualization.

Cataracts are the only complication in GALK deficiency, though very rarely pseudotumour cereberi has also been reported. GALE presentation falls on a spectrum varying from isolated hypergalactosaemia, to the severe classical galactosaemia type picture. While there are reports of motor and intellectual delays in the more severely affected, given the extremely small number of reported patients and the parental consanguineousity it is difficult to be sure these are truly features of the GALE deficiency.

**Investigations**

As discussed above the affected lactosaemic baby will classically present with differing severity of liver dysfunction. Table 1 gives a list of investigations that covers the common causes of neonatal hepatic dysfunction, while Table 2 gives the specific tests, both screening and confirmatory for galactosaemia.

The diagnosis of GALT deficiency can be confirmed by measuring the GAL-1-PUT activity using either the Beutler fluorescent spot test or an actual quantitative assay of red blood cell galactose-1-phosphate uridylytransferase activity. The later, though more labour intensive, has the advantage of being able to distinguish variants with residual activity. Both assays are erythrocyte based and invalidated by recent blood transfusions, though quantitative assays of both parents can be informative in these circumstances as they can determine potential carrier status.

**Differential diagnosis**

(1) Galactosaemia — There are few causes of galactosaemia outside Leleoir pathway defects, though any significant liver dysfunction has the potential to decrease galactose handling; an example of this is an infant with extrapathetic portosystemic shunting found to be galactosaemia post feeds.

(2) Liver dysfunction — The differential diagnosis for neonatal liver dysfunction is far wider, ranging from infections to structural abnormalities e.g. biliary atresia, to inborn error of
metabolism (IEM). Thus any child with acute liver dysfunction in the neonatal period should be thoroughly investigated both biochemically and radiologically. Of the IEMs, urea cycle, fatty acid oxidation disorders and organic acidemias can present with impairment in liver function. However the inborn error that most closely mirrors galactosaemia’s presentation is tyrosinaemia type 1 which also presents in the neonatal period with acute liver and renal tubular dysfunction. The investigations listed above while not an exhaustive list are designed to exclude most of the more common causes (see Table 1).

**Management**

The initial management of classical galactosaemia is systemic support for the acute toxicity and the withdrawal of exogenous galactose. Withdrawal should be instituted immediately if galactosaemia is considered with suitable milk formulations being either soya based preparations, or in patients with a degree of acute hepatic dysfunction and possibly limited absorption, Pregestimil (which still contains traces of galactose). The support of severe liver dysfunction includes the administration of vitamin K, antacids, the maintenance of at least 6 mg/kg/min of glucose (often requiring high concentration dextrose, as fluid restriction is normally recommended).

**Chronic manifestations of galactosaemia**

Despite early dietary intervention Glactosaemic patients may still develop a number of long-term complications:

**Neurology/motor development**

Neurological manifestations linked with galactosaemia include, diffuse cerebral oedema and pseudotumour cerebri. This is

<table>
<thead>
<tr>
<th>Sample</th>
<th>Specific tests</th>
<th>Rational/finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>Reducing substances</td>
<td>Reflextion of tubulopathy seen in some metabolic conditions</td>
</tr>
<tr>
<td></td>
<td>Protein/creatinine ratio</td>
<td>Raised with tubulopathy seen concurrently</td>
</tr>
<tr>
<td></td>
<td>Urine amino acids</td>
<td>Generalized aminoaciduria in renal dysfunction especially galactosaemia and Tyrosinaemia</td>
</tr>
<tr>
<td>Stool</td>
<td>Urine organic acids</td>
<td>To insure no succinylacetone (Tyrosinaemia type 1) and organic acidemias</td>
</tr>
<tr>
<td></td>
<td>Check pigmentation</td>
<td>If reduced discuss with hepatology team re biliary atresia</td>
</tr>
<tr>
<td>Routine blood</td>
<td>FBC</td>
<td>Can show signs of haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td>U+Ees LFTs, including GGT and clotting</td>
<td>Reflecting of degree of liver dysfunction</td>
</tr>
<tr>
<td></td>
<td>Blood gas/calculate anion gap</td>
<td>Potential acidosis reflecting renal bicarbonate loss Increase anion gap indicative of accumulating cations e.g. organic acidemia</td>
</tr>
<tr>
<td></td>
<td>Urine+Blood culture/CRP/Viral serology</td>
<td>To look for infection To rule out Hep A–C, CMV, EBV and Parvovirus</td>
</tr>
<tr>
<td></td>
<td>Lactate</td>
<td>Indication of the a disorder of the respiratory chain (NB also raised in severe liver dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Ferritin/LDH</td>
<td>To insure no Haemochromatosis</td>
</tr>
<tr>
<td></td>
<td>Cortisol(fasting)</td>
<td>Assessment of adrenal function</td>
</tr>
<tr>
<td></td>
<td>CK</td>
<td>Potentially raised in a fatty acid oxidation disorders</td>
</tr>
<tr>
<td></td>
<td>Ammonia</td>
<td>To rule out urea cycle defect</td>
</tr>
<tr>
<td>Specialized blood</td>
<td>Acylcarnitine profile</td>
<td>To rule out FA oxidation disorder OA</td>
</tr>
<tr>
<td></td>
<td>Plasma AA</td>
<td>Raised phenylalanine, tyrosine and methionine expected</td>
</tr>
<tr>
<td></td>
<td>Transferrin isoelectrofocusing</td>
<td>Indicative of CDG if positive</td>
</tr>
<tr>
<td></td>
<td>Chitotriosidase</td>
<td>To look for Niemann–Pick C</td>
</tr>
<tr>
<td></td>
<td>Alpha 1-antitrypsin</td>
<td></td>
</tr>
<tr>
<td>Radiology</td>
<td>Abdominal ultrasound post fast</td>
<td>Liver, Spleen size/Hepatic vessel size/direction of flow. Bilary system</td>
</tr>
</tbody>
</table>

**Table 1**

**Specific investigations for Galactosaemia**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Sample</th>
<th>Rational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening tests</td>
<td>Urine dipstick, Galactose-1-P, Gal-1-Put, DNA</td>
<td>Reducing substances positive after a lactose containing feed galactose, Raised in Leloir pathway defects</td>
</tr>
<tr>
<td>Confirmatory tests</td>
<td>Blood lithium heparin (minimum 1 ml)</td>
<td>To look for GALT activity NB pre transfusion</td>
</tr>
</tbody>
</table>

**Table 2**
thought to be secondary to the osmotic action of increasing amount of intracerebral galactitol and has only been noted in neonates.

Some galactosaemic patients may develop a progressive extrapyramidal disorder, which tends to manifest as tremor and ataxia, though infantile onset of choreiform movements is also known. The cause is unknown but functional scanning with PET scans has shown both a decrease in activity in the cerebellum and an increase in activity in the basal ganglia; the latter being is also observed in Parkinsonian patients.

Significant involvement of the cerebral white matter has also been noted, with widespread decreases in metabolism across most of the cerebral cortex. This mirrors what has been seen on both autopsies and neuroimaging of GALT patients. Indeed up to 1/3 of patients show some signs of cerebral atrophy on MRI scanning, with a corresponding amount having abnormal EEGs. However the day-to-day correlation of these changes with the overall clinical outcome is still unclear and the precise underlying pathological mechanisms which result in these white matter changes are still unknown.

Neuropsychological/language
The structural and functional changes of the cerebral white matter underlie the verbal dyspraxia and intellectual impairment which has been witnessed in many galactosemic patients. Overall the mean IQ of patients with classical galactosaemia has typically been found to be in the range of 70–90 though normal intelligence has been noted. There is no evidence from the longitudinal studies published that there is any decline in IQ with age though this conflicts with large cross sectional studies from the early 1990s.

There appears to be a generalized impairment in both performance related IQ and verbal IQ. One area that long been recognized to cause particular problems for galactosaemics is language with 56% of patients having language difficulties with problems in articulation being particularly common i.e. verbal dyspraxia. This appears to be related to, but is not only the result, of the lower cognition found in patients. The overall impact of speech therapy on outcome in galactosaemic patients is still to be determined.

Endocrine/fertility: impairment in ovarian function was initially noted by Kaufman et al in 1979, with over 80% of female patients being observed to have hypergonadotrophic hypogonadism with increased FSH levels, often from an early age. This presents with pubertal delay or with primary or secondary amenorrhoea, with subsequent progression to premature ovarian failure. The proposed mechanisms for the ovarian failure include, the direct effect of galactose and its metabolites leading to early oocyte toxicity effects or effects secondary to hypoglycosylation of FSH, resulting in an aberrant isoform, which is unable to induce cyclic AMP activation. Recent work highlighting a reduction in anti-mullerian hormone from early in life, coupled with normal bioactivity of FSH from Galactosaemics would suggest that the reduction in ovarian function, is through primary toxicity (at least partially in utero), rather than due to secondary insensitivity. The risk of premature ovarian failure does not seem to be reduced by good dietary control, also suggesting early gonadal toxicity Some Galactosaemia women can spontaneously become pregnant however, with 55 reported cases in the medical literature.

There has been no convincing evidence of male gonadal impairment and normal testosterone levels have been seen in a number of studies.

Apart from the rise in FSH, relatively low levels of IGFBP-3 and IGF-1 have also been shown in patients of both sexes, there

### Follow up recommendations for classical Galactosaemia patients

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Frequency of review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical control</strong></td>
<td></td>
</tr>
<tr>
<td>Gal-1-P to be kept below 150 μmol/l red cells, 50 μg/ml packed cells, 5 mg/100 ml, 0.5 μmol/g haemoglobin</td>
<td>&lt;1 year, every 3 months</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td></td>
</tr>
<tr>
<td>Calcium &amp; bone profile. 25 OH Vitamin D levels should be between 70–120 nmol/L</td>
<td>1–14 years, every 6 months, &gt; 14 years, annually</td>
</tr>
<tr>
<td><strong>Endocrinology</strong></td>
<td></td>
</tr>
<tr>
<td>DEXA scanning 2 yearly during adolescence</td>
<td>At 6 months and then at 10 years and 12 years</td>
</tr>
<tr>
<td>(1) FSH/LH/estradiol</td>
<td></td>
</tr>
<tr>
<td>(2) Referral to a paediatric endocrinologist by the age of 10 years</td>
<td></td>
</tr>
<tr>
<td><strong>Gal-1-put</strong></td>
<td></td>
</tr>
<tr>
<td>Regular assessment of development and cognitive function are indicated using standardized tests—for example, Griffiths scales, Bailey scales, British ability scales. In particular, assessment should be directed towards early detection of speech impairment</td>
<td>Regular local follow up with child development centre review</td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
<td></td>
</tr>
<tr>
<td>Slit lamp examination for cataract</td>
<td>Assessment should be made at the time of diagnosis, then yearly until the age of 3. It should be then be reviewed if concerns with compliance</td>
</tr>
</tbody>
</table>

Table 3
has however been no incidence of defects in the thyroid function, cortisol or prolactin profiles of 37 patients on a lactose free diet.

**Bone metabolism/growth**

The work of Panis et al has shown a predisposition of galactosaemic patients towards generalized osteopenia in treated children. This was despite normal levels of all trace elements, calcium, 1,25-dihydroxy-vitamin D and PTH in 40 patients studied. Lower IGF-1, a stimulator of osteoblast division and matrix production, and decreased levels of carboxylated osteocalcin was found. Subsequently supplementation with a combination of vitamin K and vitamin D3 showed significant increases in prepubertal Bone mineral content on Dexascanning, leading to their proposal of regular 2-yearly assessment with Dexascanning and supplementation if required. It is to be remembered however that pubertal delay & ovarian failure will also contribute to reduced bone mineral acquisition.

Growth in galactosaemics has been controversial with prenatal growth/birth weight, found to be reduced or normal. Panis et al found decreased height velocity in female patients, with the mean corrected height when compared to mid-parental target height Z-score was less than the target height in most patients. The low IGF-1 and IGFBP-3 levels found were thought to be significant, without any apparent nutritional deficiencies being apparent in these patients. However as in the Waggoner review, there is often apparent physiological delay with eventual normal achievement in height. Careful monitoring of growth and pubertal development is recommended.

**Eyes/cataracts**

The overall frequency of cataracts was reported initially at about 30%. Nearly half of the cataracts in this study were described as “mild”, “transient” or “neonatal” and tended to resolve with dietary treatment; though one neonatal onset cataract did require surgery. However more recent reviews indicate that the rate of cataracts is lower (14%) and none had a significant impact on vision. There have been no recorded cases of development of cataracts in patients who are compliant with diet.

**Treatment**

Long-term management is dietary, with the current recommendations being to avoid lactose containing foods with no restrictions beyond this. The rational being that although fruit, vegetables and offal are known to contain small amounts of lactose, the concentration is minimal, <30 mg/day in a typical unrestricted diet to 54 mg/day in a fruit enriched diet, when compared to the endogenous production of galactose which has been calculated at >1000 mg/day in a typical adult. There are reported cases of adults homozygous for the Q188R mutation who had discontinued their diet in early childhood without apparent ill effects. Generally however the current recommendations are to continue the use of galactose restricted diet lifelong. Those patients on this diet should insure an adequate calcium intake.

**Follow up**

Ideally follow up should be based on the shared care model between a specialized regional centre and the local paediatric teams. The Current UK recommendations (Walter JH et al 1999 see Further reading) for monitoring are listed below are listed in the table above (Table 3).

**Prevention**

Unlike much of Europe and most of the United States there is no newborn screening program for galactosaemia in the UK. The rational behind this is that potentially clinical symptoms start prior to when screening is performed which is usually on days 5—7, the relative infrequency of the disease and the current lack of demonstrable impact on long-term outcome in early screened population. Against this only 79% present by 2 months, the diagnosis can still be missed in the presence of typical signs and dietary treatment is started sooner where screening is performed. While the early commencement of dietary treatment is yet to convincingly be shown to impact on neurological outcome, this must be balanced with the greater need of intensive care and longer inpatient medical care, as well as the impact on the family of having a sick infant, when with screening this is often preventable.

**FURTHER READING**


**Practice points**

- Any neonate or infant with either progressive or severe liver dysfunction should be considered to be galactosaemic and started on either a soya based formulation or progestamil until the results of the initial investigations are available.
- Initial investigation for Galactosaemia should include both gal-1-P and GAL1PUT (taken prior to any blood transfusions).
- The current recommended treatment is a lifelong minimal galactose diet, which is insured by having a lactose free diet.
- There are a number of increasingly well defined long-terms problems, that affect SOME galactosaemic children, thus children should continued to have regular reviews to identify potential problems early and institute supportive measures.