Disorders of Carbohydrate Metabolism
INBORN ERRORS OF GALACTOSE METABOLISM

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INITIAL MANAGEMENT OF SUSPECTED CASES OF INBORN ERRORS OF CARBOHYDRATE METABOLISM

TABLE 34.2-1 Possible Presenting Features of Defects in Hepatic Carbohydrate Metabolism

Neonate	Hypoglycemia, vomiting, diarrhea, lethargy, poor feeding, sepsis syndrome, lactic acidosis, jaundice, hemolysis, hypotonia, seizures, liver failure
Infant	Hypoglycemia or hypoglycemic seizure, failure to thrive, episodic vomiting, hepatomegaly, abnormal liver function tests, chronic liver disease, cataracts
Child	Hepatomegaly, failure to thrive, short stature, anomalous eating behavior/sugar avoidance, developmental delay

SUGGESTED INITIAL INVESTIGATIONS

TABLE 34.2-2 Suggested Initial Investigations
Blood/plasma/serum samples
Electrolytes
Liver function tests
Coagulation studies (PT/PTT)
Blood gases
Blood glucose
Insulin level
Lactate & pyruvate
Free fatty acid & 3-OH butyrate
Urate
Triglycerides and cholesterol
Phosphate and magnesium
Red blood cell galactose 1-phosphate uridyl transferase activity
Sugar chromatography
Urine sample
Ketones
Reducing substances
Abdominal ultrasonography

In many circumstances, an infant may be acutely unwell and in need of care prior to results of diagnostic tests being available.

The following steps should be taken while awaiting results of diagnostic investigations.

Many of these investigations will be most informative if collected at the time of hypoglycemia.

Therefore, when suspecting an inborn error of carbohydrate metabolism in a sick infant, it is important to attempt to collect the samples immediately at presentation because the opportunity for “safe” hypoglycemia may not present itself for some time.

In some cases, a controlled fast should be arranged.

Measure the blood glucose and correct hypoglycemia with intravenous (IV) glucose solutions aiming at 8-9 mg of glucose/kg/min, an infant's normal rate for hepatic glucose synthesis.

Avoid protein and lipid input until more diagnostic information is available (there may be an inborn error of metabolism other than one affecting carbohydrate metabolism).

Collect blood and urine cultures followed by empiric broad-spectrum antibiotics, *Escherichia coli sepsis is a particular association with galactosemia.*

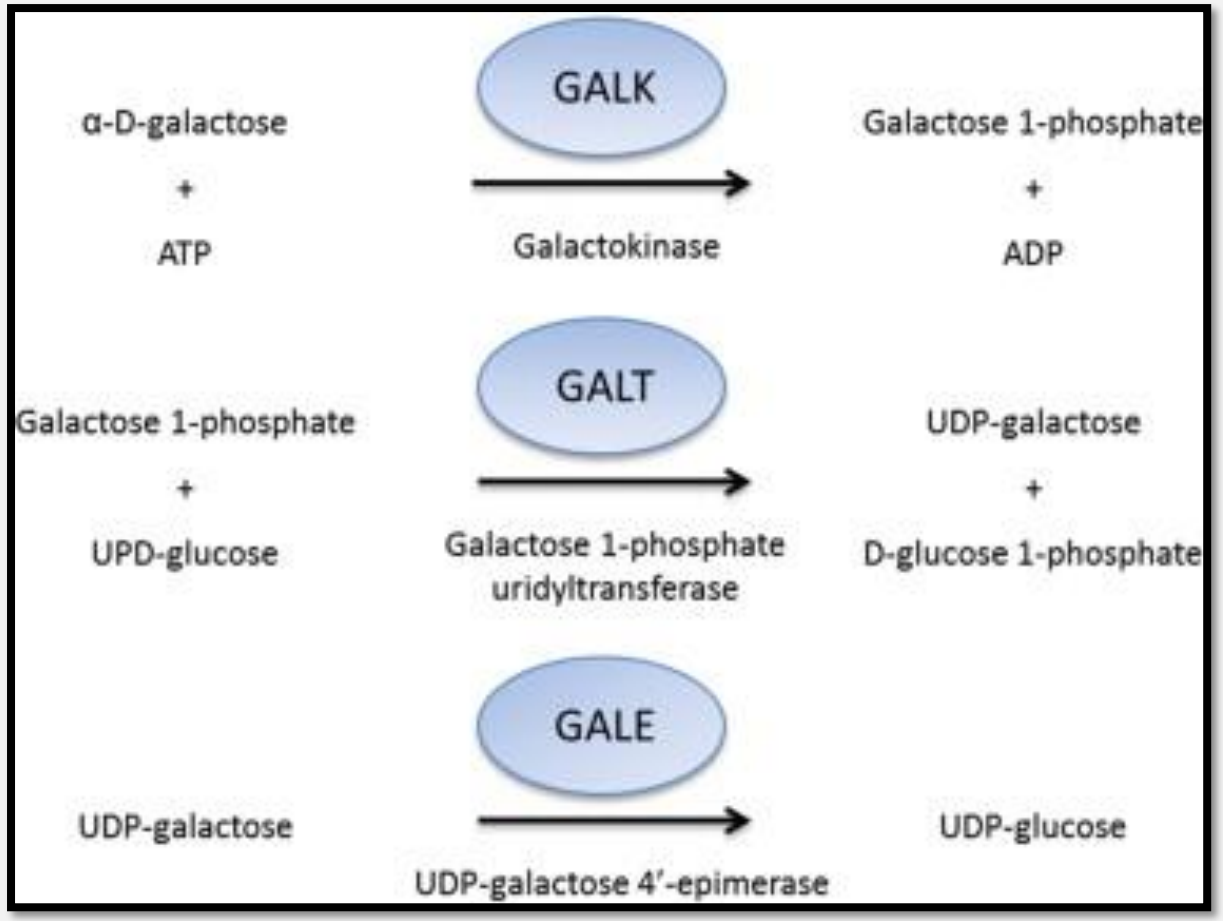
Rule out disseminated viral syndromes, particularly herpesviruses.

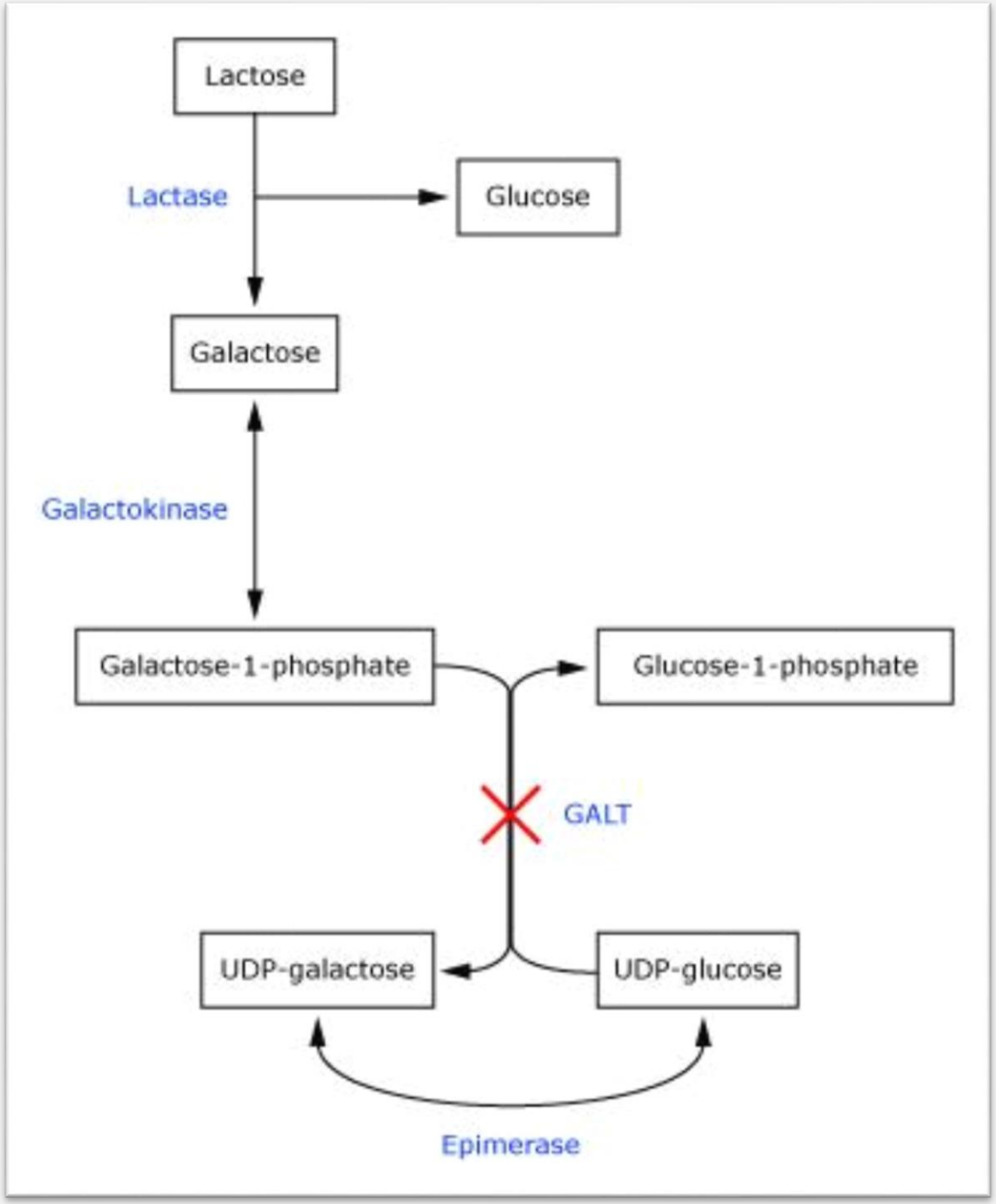
Measure PT/PTT and consider correcting coagulopathy if present.

Manage any other features of liver failure.

Provide general supportive measures such as rehydration and management of acidosis.

INBORN ERRORS OF GALACTOSE METABOLISM




Lactose
Lactase
Glucose
Galactose
Galactokinase
Galactose-1-phosphate
Glucose-1-phosphate
GALT
UDP-galactose
UDP-glucose
Epimerase

GALACTOKINASE DEFICIENCY

The first step in the hepatic metabolism of free galactose is conversion to galactose-1-phosphate catalyzed by galactokinase, deficiency of which was first described in a child with bilateral cataracts.

This has been a consistent feature in all cases described since, and it is notable that the other features of classical galactosemia do not occur.

There is no acute metabolic episode associated with this condition.

Ovarian failure and growth failure do not occur.

Galactokinase deficiency is not thought to pose neurodevelopment problems although pseudotumor cerebri has been described in a few cases.

Galactokinase deficiency is probably less common than classical galactosemia.

The diagnosis is suspected either on the basis of neonatal screening or because of infantile cataracts, and is confirmed by demonstrating deficient galactokinase activity with normal galactose-1-phosphate uridyl transferase (GALT) activity in red blood cells.

The cause of the cataracts appears to be galactitol, the product of reduction of galactose by aldose reductase.

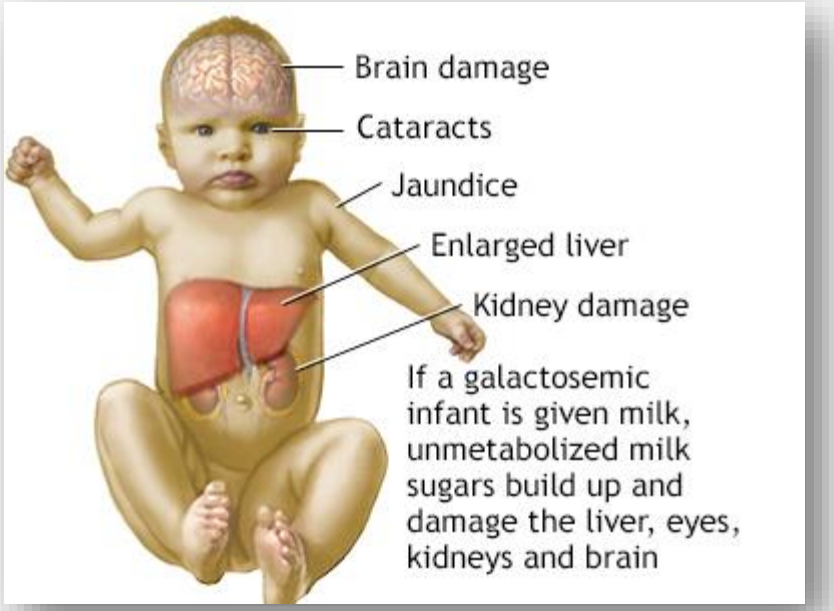
GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE (GALT) DEFICIENCY

GALT deficiency is the most common defect of galactose metabolism, and the clinical picture was first described by Goppert in 1917.

In the United States, most infants with galactosemia are now diagnosed on infant screening.

World Incidence rate:1/60000(1/30000-1/1million)

Inheritance: Autosomal recessive



Often the patients are asymptomatic at diagnosis.

Some infants present acutely within days of birth with vomiting and diarrhea, irritability or lethargy with hypotonia, and the rapid diagnosis allowed by the early neonatal screening may assist in the care of these sick infants.

If galactose ingestion continues, this progresses to hemolysis with jaundice and acidosis.

There may be acute metabolic collapse with liver and kidney failure leading to death.

Many of the fulminant early infantile cases are related to bacterial sepsis, with the causative organism most commonly being *E. coli.*

E. coli sepsis is so characteristic that any neonate so affected should be investigated for underlying galactosemia.

Other infants follow a more chronic course with poor feeding and growth, progressive liver disease leading to cirrhosis.

In surviving children, mental retardation is almost universal, although this is rarely at a profound level.

Cataracts have been observed within days of birth, but are more commonly seen later in infancy in those on an unrestricted diet.

Clinical presentations	Percentage (%)
Jaundice	74
vomitting	47
Hepatomegaly	43
FTT	29
Poor feeding	23
Lethargy	16
Diarreha	12
Sepsis	10

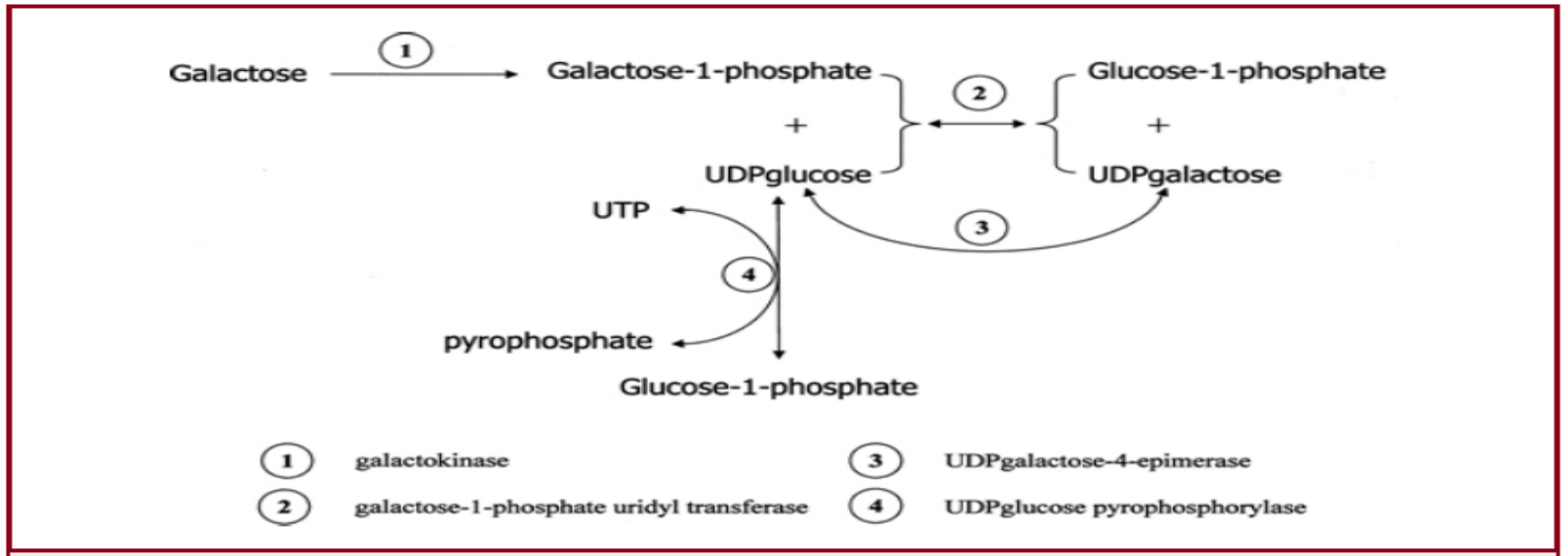


Figure 34.2-5 Metabolism of galactose to uridyl diphosphogalactose. UDP glucose, uridyl iphosphoglucose; UTP, uridyl triphosphate.

The acute metabolic syndrome is probably due to sequestration of inorganic phosphate as galactose-1-phosphate with resulting deficiency in cellular energy due to loss and insufficient restitution of ATP supply, possibly analogous to the demonstrated acute effects of fructose intake in patients with HFI.

Galactose-1-phosphate also inhibits a number of enzymes, in vitro, involved in glucose metabolism.

The acute disturbance leads to liver disease, hemolysis, lactic acidosis and renal tubular acidosis, and proteinuria and aminoaciduria.

The “Duarte” variants identified on neonatal screening have structurally altered GALT that is functionally deficient, at least in young infants.

However, after a few months, GALT activity can often be measured in the 50% range.

Development in patients with a Duarte variant is normal, and they can tolerate an unrestricted diet.

Another mild variant is commonly identified in black populations after it was noted that galactosemia is often less severe in African Americans.

Despite complete peripheral GALT deficiency, such patients are able to tolerate a normal diet.

This variant has zero GALT activity in erythrocytes, but up to 10% GALT activity when measured on liver biopsy.

The GALT gene is located at 9p13.3.

large number of mutations are identified.

The most common mutation in Caucasians causing classical galactosemia is Q188R.

The mild variant found in black populations is associated with the S135L mutation in the GALT gene.

The diagnosis is frequently made on the basis of a neonatal screen.

Positive neonatal screens should always be followed up with assay of red blood cell GALT activity or with confirmatory genetic testing.

In the unscreened population, the clinical presentation with metabolic collapse and/or *E. coli sepsis is a clue to check for nonglucose urinary* reducing substances (remember, this will become negative following the cessation of galactose containing feeds).

With clinical suspicion, milk feeds should be discontinued and IV glucose given until enzyme activity can be proven to be present.

TREATMENT

The treatment for galactosemia is dietary galactose restriction, which for an infant means removal of breast milk or formula feeds, and substitution with a galactose-free formula.

The elimination of galactose will lead to a fall in red cell galactose and urinary excretion of metabolites such as galactitol and galactinate within a few days.

However, red cell galactose-1-phosphate levels remain high and fall only gradually and red cell galactose-1-phosphate levels never return fully to normal.

The introduction of a galactose-exclusion diet allows recovery from the initial acute illness, and prevents further acute metabolic episodes.

It will reverse liver and renal dysfunction, and prevent the formation of cataracts.

Unfortunately, the diet as it exists presently appears to do little for the long-term complications of mental retardation or ovarian dysfunction in females.

In addition, growth failure, speech delay, and delayed onset neurological lesions are also not obviously affected by diet.

Waggoner has shown that the incidence of these complications in patients who start a galactose-free diet later after clinical presentation is not significantly different from those children on galactose elimination prior to the onset of symptoms because of neonatal screening or because of a previously affected sibling.

If galactose restriction does not alter long-term outcome, what is the pathogenesis of these long-term complications?

THE FIRST IS: DOES THE INSULT OR INJURY OCCUR BEFORE OR AFTER BIRTH?

Amniotic fluid of fetuses with classical galactosemia has been demonstrated to have increased levels of galactitol and cord blood has increased galactose-1-phosphate, even if the mother is on a galactose-restricted diet suggesting in-utero metabolic derangement.

To support the concept of postnatal injury, it has been noted in a number of studies that mental retardation measured by DQ/IQ is not a fixed defect, but falls progressively with age and may not be affected by the patient's compliance with galactose-restriction.

Similarly, ovarian failure common in affected females is not always manifest with primary amenorrhea; secondary amenorrhea may occur even after a successful pregnancy.

It would seem quite possible that there is a contribution to the long-term complications of galactosemia, both from antenatal and postnatal insults.

- **The second question is**: If the diet is adequately restricted, where does the toxic galactose come from?
- Are there unrevealed dietary sources of galactose, or is this some form of “autointoxication” with de novo synthesis of galactose or galactose-1-phosphate in the body?

In practical terms, a completely galactose-free diet is almost impossible.

Although the vast majority of galactose in the diet comes from milk and dairy products, there are other sources of dietary galactose.

Free galactose exists in some fruit and vegetables, and galactose can be derived from animal glycoproteins, galactolipids and galactosides.

It has been suggested that plant oligosaccharides, which contain galactose such as raffinose and stachyose, may contribute to galactose intake. However, humans do not possess the digestive oligosaccharidases to free galactose from these sugars.

On the other hand, a female volunteer with classical galactosemia had no change in galactose metabolites when taking a diet rich in fruit and vegetables known to contain free-galactose as compared to when she adhered strictly to a galactose exclusion of less than 8 mg galactose per day. This implied to the authors de novo synthesis of galactose. Recent publications have provided even stronger support for the autointoxication hypothesis.

Endogenous generation of galactose has been unequivocally demonstrated in humans, both in healthy controls and galactosemic patients and appears to account for more than 10 times the quantity of galactose supplied in a standard galactose-restricted diet.

In fact, Berry et al. demonstrated using isotopic labeling that a 50kg adult male could endogenously produce up to 2 grams of galactose per day.

It is thought that endogenous galactose production occurs from conversion of UDP-glucose via the reversible actions of UDP-galactose-4-epimerase.

- **The third question is**: Are long-term complications due in part to defective synthesis of glycoproteins and other essential galactose-containing molecules due to a relative depletion of UDP-galactose?

This again depends upon whether the flux through the pyrophosphorylase pathway can make up for the lack of UDP-galactose, which under normal circumstances appears predominantly to come from metabolism of free galactose.

Lai and colleagues also suggest that elevated cellular levels of galactose-1-phosphate as found in galactosemia inhibit UDP-hexose pyrophosphorylases and reduce the intracellular concentrations of UDP-hexoses.

Current recommendations are to maintain galactose restriction as severely as possible , especially in early infancy while the prognosis in terms of growth and development remain guarded.

UDP-GALACTOSE-4-EPIMERASE DEFICIENCY (GALE DEFICIENCY)

This condition was identified as a result of newborn screening for galactosemia.

The initial patients were noted to have normal growth and development.

The enzyme deficiency in these patients is restricted to circulating red blood cells and leukocytes, with normal activity of the epimerase enzyme in liver and fibroblasts.

This condition is entirely benign.

In contrast, a severe form has been reported in three families, each with highly consanguineous lineages. The clinical features are those of severe classical galactosemia with early metabolic dysfunction and liver disease.

Galactose restriction prevents the acute syndrome, but does not influence the growth and mental retardation observed.

Walter and colleagues have given small amounts of lactose to these patients in an attempt to maintain essential glycoprotein synthesis, as , unlike in GALT deficiency, UDP-galactose cannot be generated via the pyrophosphorylase pathway.

It appears from recent work that the two phenotypes described may in fact be two extremes of a spectrum of severity determined primarily by the mutations carried by affected individuals.

Galactosemia: Management and complications

Nutritional therapy

Immediate diet intervention(Galactose restriction) is necessary for infants with suspected galactosemia.

In infants, human milk or formula based on Lactose-free infant formulas should not be used, because they have not been proven to be safe for patients with galactosemia.

bovine milk is discontinued, and a soy-based formula is given.

Lactose-free infant formulas should not be used, because they have not been proven to be safe for patients with galactosemia.

calcium is provided by soy formula in infancy as long as appropriate volumes are taken. However, as the amount of food increases and formula volume declines after approximately one year of age, calcium supplements should be given.

Other requirements for calories, protein, vitamins, and micronutrients are similar to those of normal individuals.

MONITORING : BIOCHEMICAL STATUS

Red blood cell (RBC) galactose-1-phosphate concentration is monitored intermittently to detect serious deviations from the restricted diet.

Frequent measurement is not necessary, because levels reflect galactose intake only in the previous 24 hours, have high intraindividual variability, and do not correlate with long-term outcome.

We typically test RBC galactose-1-phosphate :

every three months in children younger than one year of age

every six months from one to three years of age

After age three years, we obtain either RBC galactose-1-phosphate or urinary galactitol levels every six months until age 14 years, then annually

MONITORING: DEVELOPMENTAL STATUS

Neurodevelopment should be assessed regularly. It should include yearly evaluation of speech and cognitive function after age two years.

Referrals are made for speech therapy as needed and for evaluation of neurologic signs if they develop.

MONITORING: CATARACT DETECTION

An ophthalmologic evaluation to detect cataracts should be performed at the time the diagnosis is made.

Eye examinations are scheduled every six months until age three years and then annually. More frequent evaluations are needed if cataracts are detected.

MONITORING: GROWTH

Postnatal growth velocity for height and weight are lower in individuals with classic galactosemia than in the general population .

Endogenous growth hormone production in girls with classic galactosemia is in the low-normal range . It is unclear whether final height is impaired and whether exogenous growth hormone or estrogen therapy plays a role.

The diet should be assessed at least annually by a dietician with expertise in metabolic disorders.

A record of the patient's diet kept by the parents for the preceding three days is reviewed at each clinician visit.

Dietary records are reviewed more frequently if growth is delayed or if dietary intake changes significantly.

MONITORING: OVARIAN FUNCTION

Primary ovarian insufficiency occurs in most females with classic galactosemia .

Approximately two-thirds of females achieve spontaneous menarche, but only approximately half of them are regularly cycling after three years, and fewer than 15 percent are regularly cycling after 10 years.

The only known factor associated with spontaneous menarche is the presence of anti-Müllerian hormone .

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol concentrations are measured in girls at 10 years of age.

If gonadotrophin concentrations are increased and estradiol level is low, the patient should be referred to a pediatric endocrinologist for consideration of estradiol therapy.

THANK YOU FOR YOUR ATTENTION