Chapter 49
Galactosemia

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Galactose metabolism involves three enzymes: galactokinase, galactose-1-phosphate uridyl transferase (GALT) and uridine diphosphate-4-epimerase (Fig. 49–1). Inborn errors of metabolism (IEM) have been described for all three enzymes. The most common inborn error in galactose metabolism is deficiency of the GALT enzyme.[1] Its incidence in North America is approximately 1 in 60,000. Galactose levels and/or GALT activity are routinely tested in all infants by newborn screening programs. Infants with elevated galactose and/or decreased enzyme activity should be referred to a biochemical genetics program that specializes in treatment of IEM. This chapter will focus on GALT deficiency since the classical form of the disease requires lifelong dietary treatment. In classical galactosemia, the GALT enzyme is not produced and the affected individual has no enzyme activity.[1]

Clinical and Biochemical Abnormalities

Neonates with untreated classical GALT deficiency present a few days after starting milk-based formula or breast milk feeding.[1] The initial symptoms include poor feeding, vomiting, and jaundice. Failure to thrive, hepatomegaly, edema, splenomegaly, and sepsis can follow. The disease is rapidly fatal if milk feedings continue. For surviving infants, mental retardation and behavioral problems are common.[1]

If a soy-based formula (i.e., Isomil, Prosobee) is initiated before serious clinical symptoms develop and if long-term dietary compliance is good, severe manifestations of this disorder can be avoided. However, follow-up studies of adolescents and adults with classical galactosemia have found that decreased intelligence (70 to 90 IQ is common) is often a problem, despite long-term dietary treatment.[2] Frequent difficulties with school performance, often secondary to attention deficit hyperactivity disorder (ADHD) or other behavioral disorders, are typical. Other late developments in well-treated individuals include speech and language problems, neurological abnormalities such as ataxia or dementia, and frequent hypogonadism in females.[3–5] The exact cause of the long-term manifestations in classical galactosemia is unknown. Prenatal exposure to galactose, endogenous galactose production, and dietary indiscretions are all potential causes of these adverse developments.[1,6,7]

Genetic Background

Galactosemia is inherited as an autosomal recessive trait. The gene, located on the short arm of chromosome 9, has been identified. To date, approximately 150 different genetic mutations causing galactosemia have been identified.[1] The most common mutation in those of European descent is Q188R. Homozygosity for this mutation always results in the classical form of the disease (0% enzyme activity). The S135L mutation is commonly found in individuals of African descent. Several variant forms of GALT deficiency have been identified. The most common is the Duarte variant, with approximately 25% of total enzyme remaining.[1]

Factors to Be Considered in Nutrition Evaluation

The most important factor affecting the length and degree of dietary treatment required for galactosemia is the amount of remaining GALT enzyme production.[8] The type of galactosemia is verified by direct enzyme analysis, genotype studies, and/or genetic mutation analysis. Knowing a child's specific mutations can provide useful information about the degree of dietary treatment and the potential long-term clinical outcome.[9] Those diagnosed with classical galactosemia must remain on a strict diet for life.[1,8] It is unclear if any dietary treatment is necessary for those with Duarte galactosemia. However, many clinics treat infants with soy-formula and lactose-free solids for the first year of life.[10] Follow-up of those with Duarte galactosemia has found no long-term developmental problems, suggesting that one year of dietary treatment is sufficient.[11]

Dietary Management

Infants with presumed classical galactosemia, identified by NBS and/or clinical symptoms, should immediately be placed on a soy-based formula to reduce galactose intake. Initiation of dietary treatment should not be postponed until final confirmation of the diagnosis becomes available.[1] Soy formulas contain a small amount of galactose (approximately 2 mg galactose/180 cc formula), but the level is considerably lower than that in breast milk or milk-based formulas (approximately 2200 mg/180 cc). Amino-acid based formulas (i.e., Neocate) contain no lactose or dairy derivatives; galactose can be completely eliminated by treating with one of these formulas.[12] However, it is unknown if use of these formulas during infancy will help prevent long-term clinical complications (S. Segal, Children's Hospital of Philadelphia, personal communication). At this time, amino acid–based formulas are not routinely recommended. Further research is needed to confirm a benefit from their use.[12,13] Casein hydrolysate formulas (i.e., Nutramigen) should be avoided since they contain more galactose than soy formula.[13]

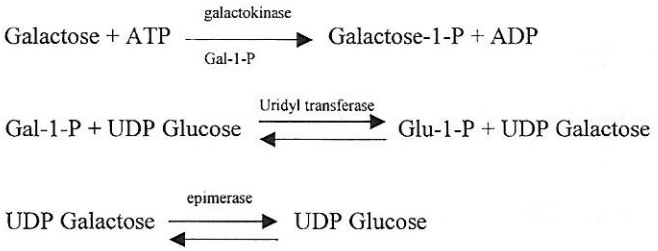

Figure 49–1. Enzymes involved in metabolism of galactose. ADP, adenosine diphosphate; ATP, adenosine triphosphate; UDP, uridine diphosphate.

Reading Food Labels

Solids are started at 4 to 6 months of age and advances in diet follow the usual progression, except all foods with lactose or galactose must be eliminated.[12] Excluded foods include all milk and dairy products (Table 49–1). Dairy derivatives (i.e., caseinates, dry milk solids) used in many processed foods are also excluded. Since galactose is stored in organs of animals, all organ meats are excluded. Parents, and later the affected child, are taught to read food labels and search for any excluded ingredients. Reference 14 provides a complete list of unacceptable foods and ingredients. Lists of acceptable baby food as well as general diet guidelines are available for professionals and parents (Table 49–1).[12–14]

Some of the dietary practices observed by the Jewish culture can be useful when looking for foods acceptable for galactosemia.[15] *Kosher* is the term used to designate a food that is acceptable in the Jewish diet. If a food product is labeled *pareve* or includes one of the symbols indicating a dairy-free product, this food is acceptable for galactosemia. Reference 14 contains a complete list of kosher symbols. Kosher symbols are voluntary for manufacturers and will not be present on all products. However, even with a kosher designation, labels still need to be checked since some foods/ingredients eliminated in galactosemia are not eliminated in pareve products.[15] Dairy-free cookbooks, typically recommended for those with dairy allergy or lactose intolerance, can also be introduced for galactosemia.[14,15] Milk substitutes (i.e., Mocha Mix, Rice Dream) are often used in these recipes, but some products labeled "lactose-free" can contain caseinates or another unacceptable ingredient.[13] Further, any product marketed to reduce lactose in dairy products (i.e., LactAid) should not be used since foods treated with these products still contain galactose.[13] Occasionally, food labels are unclear and the manufacturer will need to be contacted to verify if the product contains only acceptable ingredients.[12] Parents also need to be instructed on ways to find appropriate foods at restaurants and while pursuing various activities outside the home.[14] Ingredient lists from various national chain restaurants are available.[16]

Nutrient Supplement Needs

Because the diet for galactosemia is dairy-free, calcium supplementation is always necessary and is usually started when formula intake decreases after 1 year of age.[12,17] Poor calcium intake in galactosemia has been linked to low bone density.[18] Girls are especially prone to low bone density since bone metabolism is also affected by low estrogen production associated with hypogonadism.[18] Both adequate calcium intake and hormonal replacement therapy are necessary to prevent early osteoporosis in these young women.[18] Low intakes of vitamin D and other nutrients have been documented, and a lactose-free vitamin/mineral supplement may be necessary.[19]

Controversies in Diet Management

Despite careful elimination of all the unacceptable foods and ingredients listed in Table 49–1, the current diet prescribed for galactosemia is not galactose-free.[6,13,14,20] Galactose is bound to various carbohydrate compounds in numerous plant products. It is unclear to what extent this bound galactose is available for absorption.[6,21] Recent papers have also measured substantial free galactose in legumes and less, but significant, free galactose in some fruit and vegetables (Table 49–1).[6,22] Whole legumes (garbanzo beans, navy beans, etc.) have now been eliminated from the diet. Many baby foods have also been analyzed for galactose content. Baby food fruit, vegetables, and juice may contain significant amounts of galactose.[23,24] Baby food cereal and meat appear to contain little, if any, galactose.[24,25] A current list of acceptable baby foods is available.[14]

There is little consensus among metabolic specialists about the need to reduce or eliminate any of the other plant products. For those with classical galactosemia, some advocate eliminating all foods containing >20 mg galactose/100 g.[13] Limitation has been suggested for products with 5 to 20 mg galactose/100 g food. Some food additives are questionable. References are available to describe the composition of various additives, which may help determine their appropriateness in the galactosemia diet.[26] At this time, the actual galactose content of many foods and ingredients has not been quantitated. As more research is completed, more reliable diet recommendations should become available.

Lactose in Medications

Lactose is often used as an extender in prescription and over-the-counter medications and dietary supplements. Product labels must be evaluated and/or the *Physician's Desk Reference* (PDR) should be consulted.[8] If there is doubt about the inactive ingredients in any medication, the manufacturer should be contacted. Usually appropriate drugs can be found without added lactose; however, some classes of medications may not have lactose-free alternatives (i.e., medications for ADHD). In these cases, the necessity of the medication and the length of treatment must be weighed against the additional intake of galactose. In many cases, the amount of galactose ingested with medications is insignificant compared to the amount produced by endogenous production.[8]

Monitoring and Follow-up

All individuals with classical galactosemia should be followed by a clinic specializing in the treatment of IEM.[1,8] Clinic visits should include a physical exam, nutrition and genetic counseling, and laboratory monitoring. Referral to appropriate specialty clinics for psychological and speech evaluations is necessary at an early age so that any necessary therapies can be initiated. All girls should be seen by an endocrinologist before the age of 10 to evaluate the need for hormone replacement.[8] Ophthalmological evaluations may be needed if there is a concern about cataracts. Psychiatric treatment may become necessary to manage attention or behavioral issues.

Laboratory tests are available to assess the degree of metabolic control in this disorder. The most common laboratory assessment for galactosemia is red blood cell galactose-1-

Table 49–1. The Galactose-Restricted Diet

Foods Permitted	Foods Not Permitted	Questionable Foods
Milk Substitutes	*Milk and Milk Products*	*Milk Substitutes*
Soy formulas made with soy protein isolate: Isomil, Prosobee, Nursoy	Breast milk	All soy "dairy" products: soy milk, soy cheese, soy based frozen desserts
Nondairy cream substitutes without caseinates	All animal milks and milk products: buttermilk, cream, sour cream, yogurt, ice cream, ice milk, sherbet, butter, cheese, cottage cheese, cream cheese	
Nondairy frozen desserts containing no dairy products (i.e., Rice Dream, fruit ices)	Casein hydrolysate–based formulas, i.e., Nutramigen	
	Casein, milk solids, lactose, whey, milk fat	
Protein Foods	*Protein Foods*	*Protein Foods*
Plain meats, fish, poultry—without added milk products	Breaded or creamed meat, fish, poultry	Nonfermented soy products (i.e., meat analogs, tofu)
All-meat frankfurters, sausage, cold cuts	Organ meats or meat by-products	All seeds: pumpkin seeds, sesame seeds, etc.
Eggs without milk or milk products	Canned fish containing hydrolyzed protein	
Nuts, nut butters	Processed meats with added milk products	
	Fermented soy sauce, or soybean products in which enzyme processing is used (i.e., tempeh, natto)	
	Legumes (dried beans and peas): kidney, pinto, navy, etc.	
Fruit and Vegetables	*Fruit and Vegetables*	*Fruit and Vegetahles*
Any fruits and vegetables—fresh, frozen, canned, dried—unless processed with lactose or milk products	Fruit with milk, cream, or any milk products	Fruits and vegetables with free galactose levels above 20 mg/100g*: most tomato products, watermelon,
	Vegetables with milk, cream, or any milk products figs, papaya, etc.	Fermented vegetables: pickles, sauerkraut
Grains and Breads	*Grains and Breads*	*Grains and Breads*
Cooked and dry cereals without milk, lactose, or milk products added	Dry cereals with added whey, casein, or milk products	Baked products made with soy flour or flours made from seeds (i.e., sesame flour)
Breads, rolls, buns without milk, milk products, or lactose added (i.e., French, Italian bread)	Breads, rolls, buns, cakes, cookies, crackers, or any baked products with added milk or milk products	
Crackers, saltines, biscuits, cookies without lactose or other milk products added	Bisquick, pancake mixes containing milk products	
Flour or corn tortillas without milk or milk products added		
Macaroni, noodles, spaghetti, rice		
Fats	*Fats*	*Fats*
All vegetable oils—soybean, corn, olive, cottonseed, safflower, peanut, canola, etc.	Butter, cream, sour cream, milk fat	None
Margarine without milk or milk products added	Margarines with added milk or milk products	
Vegetable shortening, lard, suet		
Mayonnaise, milk-free salad dressings		

(*continued*)

Table 49–1. The Galactose-Restricted Diet (*continued*)

Foods Permitted	Foods Not Permitted	Questionable Foods
Beverages	*Beverages*	*Beverages*
Carbonated drinks	All drinks containing any dairy product	Juice made from questionable foods: tomato, orange, papaya, etc.
Artificial fruit drinks without lactose, milk-based extenders		Coffee
Fruit and vegetable juices, except those made from questionable foods.		
Tea		
Miscellaneous	*Miscellaneous*	*Miscellaneous*
Sugar, corn syrup, molasses, plain carob, maple syrup	Milk chocolate, white "chocolate," caramel, others with added milk.	All chocolate products except milk chocolate: semisweet, cocoa, dark chocolate, cocoa butter, etc.
Pure MSG, and spices without added lactose, dairy-based extenders	Cocoa mixes or syrups with milk products	Some vegetable gums are questionable (i.e., tragacanth gum)
Clear candies, gum drops, marshmallows, chewing gum, fruit pectins	All candies and sweets with milk products	Carageenan
Pure horseradish	Hydrolyzed protein	Honey
Caramel coloring		Equal tablets
Saccharin, Nutrasweet, liquid Equal		Hydrolyzed vegetable protein (HVP) or other soy-based additives
Most vegetable gums: Arabic, guar, xanthan, etc.		Worcestershire sauce
Dough conditioner, modified food starch		

*Reference 13 has an extensive list of the known galactose content of various fruits and vegetables.
Adapted from References 13, 15, and 16.

phosphate (RBC Gal-1-P).[8,12] Red blood cell Gal-1-P is the precursor that accumulates in cells deficient in GALT activity (Fig. 49–1). In classical galactosemia, high levels of Gal-1-P will be present at diagnosis and may take several months to decrease to the treatment range.[1] For those on dietary treatment, the upper limit for RBC Gal-1-P levels is 5 mg/dL.[8] It is controversial whether those with Gal-1-P levels consistently above the treatment range can benefit from stricter diet control.[6,8,13,27,28] Singh et al. found that the incidence of long-term complications increases in individuals with Gal-1-P levels consistently above 3.5 mg/dL (R. Singh, Emory School of Medicine, Atlanta, personal communication). Others have found no correlation between Gal-1-P levels and the clinical outcome.[29,30] Policies vary, but some clinics eliminate fruit, vegetables, and other foods with a higher galactose content when Gal-1-P levels are above 3 to 4 mg/dL.

Recent studies suggest that the genetic mutations may dictate the degree of galactose restriction required by that individual. Those homozygous for Q188R with 0% enzyme activity may need stricter dietary treatment to reduce the chance of developing late-term complications (R. Singh, Emory School of Medicine, Atlanta, personal communication). Further research is necessary to determine if tighter dietary control will benefit those with galactosemia. Some studies suggest that galactose from endogenous sources is a far greater source of elevated galactose metabolites than is diet.[7,31,32] Stricter dietary control may do little to overcome this larger galactose source.

Despite its limitations, comparing Gal-1-P values from a single individual can be useful. With good dietary control, each child will have his or her own range of Gal-1-P levels. Any significant increase from a child's usual Gal-1-P levels should be investigated. Often, these increases can be traced to an increased intake of galactose when a manufacturer changes food or medication ingredients. The frequency of Gal-1-P monitoring depends on the age of the child, the degree of enzyme activity, and the dietary compliance. A typical monitoring schedule may include checking RBC Gal-1-P every 1 to 3 months during the first year of life, with decreasing frequency as the child ages. For compliant teenagers and adults, yearly RBC Gal-1-P assessment may be sufficient.[8]

Galactitol has been suggested as a possible addition to the monitoring protocol.[33] Galactitol is a breakdown product of galactose. Plasma and urine elevations correlate with the amount of remaining enzyme activity, but high intraindividual variability may limit the usefulness of galactitol as a dietary marker.[34] Little consensus exists about the best monitoring protocol for galactosemia, and policies differ among clinics. Monitoring of galactose metabolites must be tailored to each individual.

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