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Review Article

An Updated Review of the Long-Term Neurological Effects of Galactosemia

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Classical galactosemia is an autosomal recessive condition in which there is near total absence of the activity of galactose-1-phosphate uridyltransferase. Patients with this condition have substantial motor, cognitive, and psychiatric impairments despite dietary treatment. A characteristic pattern of biochemical abnormalities is observed in patients with this disorder. Galactose-1-phosphate, the substrate of galactose-1-phosphate uridyltransferase, accumulates within cells, and surplus galactose is reduced to galactitol or oxidized to galactonate. Using sophisticated mass spectrometry, these compounds as well as free galactose can be measured in plasma and in urine. It is clear that initiation of dietary restriction of galactose in the newborn period produces reversal of hepatic, renal, brain, and immune dysfunction, along with reduction of the accumulated galactose metabolites. However, the neurologist should be aware that chronic and progressive neurologic impairments occur even in patients spared these neonatal symptoms. The purpose of this review is to summarize current information about neurologic complications of galactosemia and what is known, and still unknown, about its pathophysiology.

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History: Galactosemia Identification and Screening

Classical galactosemia was first described by von Reuss in 1908 [1]. In the mid 1950s, Komrower et al. demonstrated the accumulation of galactose-1-phosphate in red blood cells [2], and the condition was enzymatically defined as a deficiency of the galactose-1-phosphate uridyltransferase (GALT) enzyme by Kalckar in 1956 [3]. Before this enzymatic characterization, Mason and Turner demonstrated that restriction of dietary galactose could alleviate the acute neonatal symptoms [4]. During the 1960s, an enzyme assay was developed by Beutler which could be used to screen the same dried blood spot specimens collected for phenylketonuria screening [5]. Modifications of this screening test are used in all 50 states of the United States as well as many European countries. However, the initial expectations that early ascertainment and dietary restriction would result in a normal adult individual were tempered by the mid 1980s when it became clear that adverse long-term outcomes continued to occur, even in patients with well-documented compliance with the recommended galactose-restricted diet [6-9].

Transient hypergalactosemia, which has several causes, and two other genetic causes of galactosemia, caused by defects in galactokinase and uridyl diphosphogalactose-4-epimerase, are rarer, generally lack neurologic manifestations, and are not addressed in this review.

Genetics and Epidemiology

Galactosemia is a relatively rare inherited enzyme deficiency with variable worldwide incidence reported between 1:30-40,000 in Europe [10] and 1:1,000,000 in Japan [11]. The incidence in the United States, with most cases ascertained by newborn screening, is currently estimated at 1:53,000 (National Newborn Screening and Genetics Resource Center; 2002 Newborn Screening and Genetic Testing Symposium).

The GALT gene, localized on 9p13, is a relatively compact gene with 11 exons spanning 4 kilobases [12]. One hundred sixty-seven mutations have been identified (http://www.emory.edu/PEDIATRICS/medgen/research/db.htm). The most prevalent mutation in Western popula-

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tions is Q188R, in which an A to G transition in exon 6 converts a glutamine residue near the catalytic site to an arginine. Expression of this allele in yeast systems produces no detectable catalytic activity [13,14]. Several other relatively common mutations have been characterized, the most intriguing of which is S135L, the mutation present in both African-American and African blacks [15,16]. This mutation has greater residual activity in hepatocytes and is associated with a different pattern of ability to oxidize galactose [16-18] as well as a milder phenotype [19]. A much more common variant, so called "Duarte galactosemia," is also identified primarily by newborn screening. The Duarte Variant denotes a compound heterozygote for a classical allele and another allele with partial GALT activity, which results in biochemical changes during early infancy, but no evidence of neonatal or long-term morbidity [20].

Acute Neonatal Presentation and Diagnosis

Presentation

The natural history of classical galactosemia is that lethargy, poor feeding, jaundice, and hepatomegaly appear within days of the initiation of milk feedings. Progression of this acute neonatal toxicity syndrome may include the development of *E. coli* septicemia in the second week of life, coagulopathy, hyperchloremic metabolic acidosis with aminoaciduria, and vitreous hemorrhage [21]. Cataracts may be present, but may be difficult to identify. Neurologically, these patients may develop encephalopathy and signs of increased intracranial pressure with cerebral edema, usually after several days of more nonspecific signs. In the United States, many cases are ascertained because of newborn screening, but nonspecific signs may precede diagnosis by several days [22]. Diagnosis based on clinical suspicion is the primary mode of ascertainment in England, and selective screening has demonstrated merit in a Canadian population [23]. As newborn screening programs transition to screening at 24 hours of age and reporting of results within the first week, the utility of newborn screening in identifying infants in the early stages of clinical evolution is likely to increase.

Diagnosis

The gold standard for diagnosis is the demonstration of near total absence of GALT activity in red cells. Transfusion of red cells from a normal donor can interfere with this determination. Measurement of accumulated galactose-1-phosphate in red cells has diagnostic utility even if dietary galactose has been withdrawn, although benign variants can also have increased gal-1-P levels, particularly if the infant is still consuming galactose. Examination of the urine for reducing substances lacks both sensitivity and specificity [24], but can certainly raise sufficient clinical suspicion in a symptomatic infant to trigger further evaluation and empiric treatment. Deoxyribonucleic acid (DNA) analysis is rapidly available for several common mutations, including Q188R [25], and has been used in some newborn screening programs to refine the screening process. As with other mutation-selective DNA-based assays, because of the large number of distinct mutations, a positive result has predictive value, but a negative result does not exclude disease resulting from other mutations. Prenatal diagnosis is available for couples with a known family history of galactosemia [26], and carrier screening for a known GALT mutation is highly effective in defining risk.

Non-neurologic Sequelae

Growth

Growth is generally delayed in most patients with galactosemia, but final height-for-age is not significantly less than the general population, although females may be more likely to have short stature [8].

Eyes

Cataracts have been reported in up to 30% of patients with galactosemia, and they usually resolve with galactose restriction [8]. Cataracts are one of the few complications of galactosemia with a known pathophysiology. Galactitol, produced by reduction of free galactose by aldose reduction, produces swelling of lens fibers. Adolescents and adults who include higher amounts of galactose in their diet may rarely develop cataracts that interfere with ability to function and may benefit from lensectomy and intraocular lens placement. A less well known, but visually more devastating ophthalmologic complication is vitreous hemorrhage during the acute neonatal syndrome [21].

Ovarian Failure

Hypergonadotropic hypogonadism is common in females with galactosemia but has not been reported in males [8,27]. The spectrum varies from severe primary ovarian failure requiring hormone support in order to achieve secondary sexual characteristics to premature menopause. Pregnancies without hormonal intervention have been reported [8,28]. The mechanism of ovarian dysfunction is unknown, but it has been hypothesized that chronic exposure to galactose-1-phosphate and galactitol may directly damage the ovaries [29]. Significantly, from a pathophysiologic standpoint, in women with galactosemia, follicular stimulating hormone (a glycoprotein) isoforms are qualitatively abnormal, with apparently reduced terminal galactosylation [30]. Females with classical galactosemia require monitoring of gonadotropin levels and initiation of estrogen and progestin support as needed. Menses management may require modification of

hormone regimens in females with cognitive or motor impairment. There is no evidence that any current interventions preserve ovarian function.

Neurologic Sequelae

Acute Elevated Intracranial Pressure in Infants

Galactosemia must be considered in the differential diagnosis of an infant with diffuse cerebral edema, presenting with a bulging anterior fontanel, in the setting of poor feeding, jaundice, and hepatomegaly [31]. Animal models have suggested that the mechanism of cerebral edema may be that elevations in brain galactitol concentrations and alterations in glucose, adenosine triphosphate, and phosphocreatine levels increase osmolality [32]. Magnetic resonance spectroscopy has revealed elevated cerebral galactitol levels in infant brain in vivo [33]. Cerebral edema in galactosemia patients responds well to dietary galactose restriction [34]. The mechanism may be similar to that reported in a rat model with intact GALT but excessive dietary loading, in which galactitol accumulates in peripheral nerves and produces edema with increased pressure and eventual demyelination [35].

Cognitive Impairment: Gender Effects and Possible Regression With Age

Multiple studies report that mean intelligence quotient (IQ) scores are reduced in galactosemic children and adults [7-9,33,36-41]. Differences between studies result from a variety of factors. For example, differences in screening and diagnostic practices mean that the initiation of dietary treatment may vary systematically among countries. Other important differences include test batteries used and study design. For example, in large questionnaire-based studies [8], multiple testers make inter-rater variability an issue. In addition, responder bias may occur. A more closely controlled but more limited design is testing of a convenient or captive sample by a single or standardized set of psychometricians [9,41]. A consistent observation has been that cognitive function does not appear to relate strongly to time of diagnosis, initiation of treatment, or dietary compliance [8,37,40,42].

Evidence related to a gender effect has been inconsistent. Waggoner et al. obtained developmental and IQ scores on 298 patients. Mean IQ scores of females ages 10-16 and >16 years were significantly lower than males [8]. Kaufman et al. failed to identify sex differences in the broad cognitive ability scores assessed in 40 children and adults by the Woodcock-Johnson Revised tests [38].

A number of cross-sectional studies have demonstrated lower IQ scores in adults than pediatric patients [9,43], but because cross-sectional data often contain unmeasured confounders, this constitutes weak evidence of neurodegeneration. Waggoner's study, which obtained data from structured questionnaires, included responses from 88 patients tested on more than one occasion. These data revealed that mean IQ scores of galactosemia patients declined by 6.2 points from age 3-5 to age 6-9, and by 4.4 points from 6-9 to 10-16 years [8]. Another recent cross-sectional study, restricted to patients with the Q188R GALT mutation, revealed reduced IQ, particular difficulties with word retrieval and executive function, but did not support the hypothesis that IQ progressively declines. These authors suggested that older patients may diverge more from their peers in performance-IQ related tasks as a result of slow processing speed [41].

Speech Apraxia Commonly Occurs

Speech difficulties are common in galactosemia. One study reported that 56% of patients with galactosemia over 3 years of age have difficulties with speech, with 92% of these patients described as having delayed vocabulary [8]. Nelson et al. reported that, of 24 galactosemic patients surveyed, 62% had speech pathology, primarily verbal dyspraxia [44], or developmental apraxia of speech, defined as the impairment of motor programming of speech musculature for the willful purpose of producing sound [45]. Verbal dyspraxia is often refractory to standard speech therapies [46].

Galactosemic patients with speech difficulties had significantly lower developmental quotient (DQ) and IQ scores than patients without speech difficulties [8,44]. Lower DQ/IQ scores and speech pathology could independently reflect more severe neuropathology. Alternatively, speech and motor difficulties may interfere with accurate testing. As in other adverse outcomes in galactosemia, there is not good evidence that development of speech difficulties correlates with age of initiation of dietary therapy, severity of presenting symptoms, or compliance with dietary therapy [8,44].

Motor Function—A Subgroup Develops More Severe Ataxia and Tremor

Despite early treatment initiation and optimal dietary compliance, approximately 10-20% of galactosemia patients develop more severe and progressive ataxia and tremor [7,8,38,47-49]. For example, in a cohort of 45 well-studied patients, 12 had tremor, ataxia, and dysmetria with no distinguishing neuroimaging, neurophysiologic, or biochemical findings and no significant differences in mean cognitive scores [38].

Seizures Are Uncommon

Seizures have been described rarely in galactosemia. Two siblings with galactosemia developed seizures in adulthood [48]. It is possible that these seizures are unrelated to galactosemia, given the low prevalence of reported seizures.

Pathophysiology of Neurologic Dysfunction in Galactosemia

The chronic manifestations of galactosemia most likely result from assaults from multiple fronts, including possibly intoxication and cell dysfunction or death due to specific metabolic derangements and secondary disturbances in myelin production. The heterogeneity of presentation may be influenced by the inherited GALT alleles and amount of GALT activity, by the individual's endogenous production of galactose, by the individual's ability to oxidize galactose, and by the function of alternative enzymes in the metabolic pathways [22]. This article will review issues of metabolic intoxication as well as recent research from animal models, postmortem tissue, neuroimaging, and genetic studies with regard to these theories.

Metabolic Derangement and Intoxication

In the presence of sufficient GALT activity, galactose is transported into cells then phosphorylated by galactokinase, effectively trapping it as galactose-1-phosphate (gal-1-P) (Fig 1). With near total absence of GALT, gal-1-P accumulates and results in product inhibition of kinase. Accumulating free galactose is diverted into secondary pathways that produce either galactitol [50] or galactonate [51]. These substances have been demonstrated in affected organs [33,52,53]. Thus, one possibility is that these substances cause direct damage to vulnerable subpopulations of neurons, for example, Purkinje cells, or to white matter.

A chronic intoxication theory has been proposed with either exogenous galactose intake from poor dietary compliance or hidden environmental sources [54] or from endogenous synthesis of galactose [55] resulting in increased long-term exposure. This exposure could theoretically cause progressive neurologic symptoms in some or most patients, but mechanisms by which this impairment occurs remain under investigation.

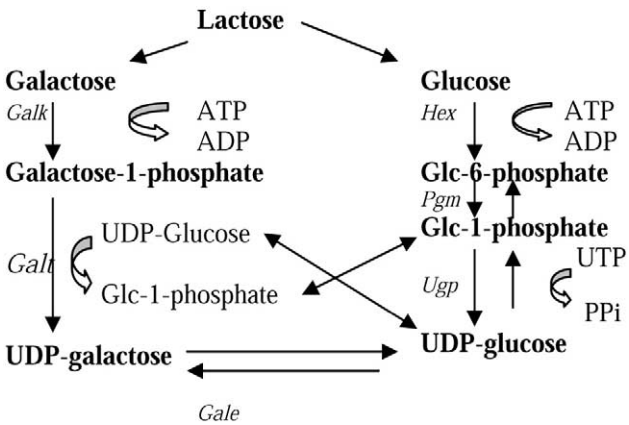

Figure 1. The Leloir pathway of galactose metabolism and the uridine diphosphate (UDP)-glucose pyrophosphorylase pathway. Galk, *galactokinase;* galt, *galactose-1-phosphate uridyltransferase;* gale*UDP-galactose 4-epimerase;* hex, *hexokinase;* pgm, *phosphoglucomutase;* Ugp, *UDP-glucose pyrophosphorylase.*

In utero toxicity has also been suggested [56], possibly due to elevated galactitol levels. Evidence for this theory comes from observations of fetal cataracts and early liver dysfunction. In utero exposure to galactose was demonstrated by high levels of gal-1-P in the fetus and galactitol in the amniotic fluid in mothers placed on strict galactose-restricted diets [57,58]. Magnetic resonance spectroscopy has documented markedly elevated brain galactitol levels in four newborn infants aged 6 to 15 days compared with age-matched control subjects [33]. However, in the eight galactosemia patients aged 1.3 to 47 years, no elevation was identified in six, and slight elevation in just two. A prior magnetic resonance spectroscopy study of six adults disclosed no elevation [59]. This finding suggests that although galactitol could cause early, static central nervous system injury, it would be unlikely to cause progressive neurologic impairment.

Dietary control and levels of gal-1-p do not appear to account for variance in cognitive outcomes [8,37,40]. However, a recent study assessing total body galactose oxidation with a breath test after a ^{13}C-galactose bolus found three related biochemical abnormalities that were more common in galactosemia patients affected neurologically with speech dyspraxia. In 24 patients with galactosemia who underwent speech evaluation, the 15 with speech dyspraxia had a significantly lower cumulative percentage dose $^{13}CO_2$ in breath, increased erythrocyte gal-1-P, and increased urinary galactitol. These abnormalities were also influenced by GALT genotype [60].

Magnetic resonance spectroscopy studies have not found evidence of abnormal cerebral energy metabolism in patients with diet-restriction treated galactosemia [33,59].

Evidence From Animal Models

Two types of animal models have been employed to study galactosemia. In the first, animals with intact GALT are exposed to elevated levels of galactose or other metabolites. The second is a genetic knockout of the GALT enzyme.

Feeding excess galactose to rats with intact GALT reduces levels of inositol [61,62] and increases galactitol in synaptosomes [63]. Dogs fed excess galactose for 44 months display multiple peripheral nervous system abnormalities [64]. The relevance of these findings has been called into question given that these animal models had no enzyme defect, that excess exogenous exposure may not mimic the treated human disease, and that changes resulting from malnourishment can not be ruled out [65].

A galactosemia model, the GALT deficient knockout mouse, lacks measurable GALT activity and develops biochemical features similar to those in humans including high levels of galactose-1-phosphate. However, these mice do not develop cataracts, they can reproduce normally, and they appear to have no neurologic phenotype. These mice have minimal levels of tissue galactitol. This finding

suggests that GALT deficiency is necessary, but not sufficient, to cause human disease and that both elevated galactose-1-phosphate and galactitol may be necessary for the human phenotype [66,67].

Autopsy Studies

There are only published postmortem examination data on two cases. Although these are biased toward more severe phenotypes, their importance arises from direct observations of gray and white matter damage, yielding insights into selective neuronal vulnerability in galactosemia. Future postmortem examination studies may be invaluable, and basic research should focus on identifying mechanisms of regional and neuronal injury identified in these studies.

In 1962, Crome provided a detailed pathologic report of a severely impaired male with galactosemia and partial dietary restriction who was institutionalized and died of pneumonia at age 8 years [68]. This individual was able to walk with a stiff gait, to feed himself with hands but not utensils, was incontinent, socially withdrawn, and had no spoken language. Postmortem findings included diffuse white matter gliosis, particularly around the ventricles and in the brainstem, and diffuse pallor, particularly in the cerebrum. There were many areas of chronic, focal necrosis in the white matter. Cerebellar Purkinje cells were markedly depleted, largely sparing the granular layer. There was neuronal loss in the dentate nuclei and inferior olives. Extracellular fat globules were observed in the globus pallidus. This apparent neuronal selectivity is intriguing given findings in rat brain of somewhat more abundant GALT gene expression in cerebellum [69] as well as the prominent ataxia and tremor in some galactosemia patients.

Similar findings were reported by Haberland et al. in another severely impaired patient, untreated until diagnosis at age 13 years, who died at age 25 years of pneumonia [70]. This patient had severe mental retardation, extrapyramidal motor symptoms, and epilepsy. Microcephaly, cerebral cortical neuronal degeneration, cerebral white matter atrophy and sclerosis, and cerebellar findings similar to Crome's case were described. In addition, these authors reported abnormal levels of glycoproteins and glycolipids.

Central Nervous System White Matter

Both of the postmortem examination reports [68,70] and multiple neuroimaging studies demonstrate that white matter is abnormal in galactosemia [33,38,39,71]. The mechanism for this is unclear. It is possible that GALT deficiency leads to defective synthesis of glycoproteins and galactolipids critical for normal myelin, possibly as a result of defective transfer of galactose from uridine disphosphate-galactose (UDP-gal) [72].

The main current limitation of neuroimaging research is that the diffuse central nervous system white matter change has not been quantified and thus is not available to be analyzed as a continuous variable in regression analyses with an outcome like IQ. Because diffuse white matter abnormalities are almost universally present [33,38,71], this also cannot be used as a class variable for group comparisons of various measures of impairment. For example, Kaufman et al. reported that magnetic resonance imaging abnormalities in 40 subjects "(did) not correlate with cognitive outcomes" [38]. White matter was diffusely abnormal in 37 of 40 patients. Using the overall cognitive function as an outcome and "abnormal white matter" as a class predictor, this study would only have about a 7% power to detect a meaningful 10-point difference. They also used presence or absence of enlarged ventricles, focal lesions, and mild cerebral atrophy and found "no differences" in neurologic outcomes. A study using magnetic resonance spectroscopy did not identify changes in choline, *N*-acetyl aspartate, or myoinositol. However, only two spectra were performed on white matter regions [33]. These comparisons would also have low statistical power.

That the abnormal-appearing white matter in galactosemic patients also functions abnormally is supported by findings of prolonged latencies of somatosensory evoked potentials [73]. In 60 galactosemia patients, somatosensory evoked potentials manifested one or more abnormalities (absence of expected peaks, prolonged latencies) in 34 (57%). The proportion of patients with abnormalities did not differ among the 12 patients with ataxia and tremor vs the less neurologically impaired patients. Cognitive function also did not differ between those with normal somatosensory evoked potentials and those with abnormal somatosensory evoked potentials.

Future neuroimaging or neurophysiology research into galactosemia pathophysiology may benefit from the identification of newer quantitative variables for use in more rigorous statistical analyses.

Influence of Genotype on Cognitive Outcome

Although galactosemia is an autosomal recessive disorder caused by mutations at a single major locus, the GALT gene, there appears to be considerable biochemical and phenotypic heterogeneity among patients who share common mutations studied. The basis for this variation is not understood. There is controversy in the literature over whether cognitive outcome, e.g., IQ scores, is correlated with genotype [37,40,42,74]. The most common mutation, the Q188R mutation, has been the most studied.

Two studies provide evidence that homozygosity for Q188R is associated with poorer cognitive outcome. Elsas et al. found a poorer outcome in 22 patients homozygous for the Q188R mutation, compared with 20 patients who were compound heterozygous for Q188R plus another disease-causing allele [75]. Shield et al. found a significant, 20 point lower IQ in patients homozygous for

Q188R, vs those with Q188R plus an alternate mutation. There was no correlation between galactose-1-P levels and IQ [40].

In contrast, two other studies found higher average cognitive function in patients homozygous for Q188R, although these differences fell short of statistical significance. Cleary et al. found no significant difference in IQ, comparing nine homozygous for Q188R, median IQ 81, and six heterozygous median IQ 72 [37]. Kaufman et al., using the Woodcock Johnson Broad Cognitive score, found a score of 75 (S.D. 16) in 38 patients homozygous for Q188R and 67 (S.D. 25) in 21 patients heterozygous [42]. The power for these two negative studies to detect a statistically significant difference ($P < 0.05$) in those samples was less than 25%. In addition, the non-Q188R/Q188R comparison groups in these studies are different. Thus the influence of the most common genotype on phenotype remains unclear. What is clear is that, while the mean IQs in these studies are all low, the standard deviations are comparable to those in the general population. This finding indicates that there is substantial heterogeneity among subjects with the same GALT genotype, which is similar to what has recently been described in other autosomal recessive major gene disorders [76,77].

Treatment: Standard of Care, Controversies, and Clinical Trials

Treatment of Symptomatic Infants—Standard of Care

Symptomatic infants or infants with highly suspicious newborn screening results should be evaluated promptly, and galactose-containing formulas should be withdrawn. Supportive care with intravenous fluids, phototherapy, antibiotics, and treatment of coagulopathy should be initiated as needed. Despite the nearly universal availability of newborn screening in the United States, infants with classical galactosemia still die. The use of galactose-limited formulas because of family preferences or early symptoms may completely mask the initial clinical presentation. Subsequent to diagnosis, during infancy, dietary management with galactose-free formula is straightforward.

Long-term Nutrition Management—Standard of Care and Recent Issues

Once solid foods are initiated, and when infant formulas are weaned, nutritional issues become more complicated. An ideal, standard practice has been to reduce or attempt to eliminate galactose in the diet. However, no person, unless completely nourished with artificial formula, has ever been on a galactose-free diet. Traditional means to monitor dietary compliance have not proven clinically useful, even in some noncompliant individuals.

Prior strict dietary recommendations are tempered by data from recent technical advances that have increased the precision of estimates of endogenous synthesis of galactose [78-81]. These studies demonstrate that endogenously synthesized galactose substantially exceeds the dietary amounts acquired in fruits and vegetables [82], in galactose-containing medications, or from other sources in a strict diet. Moreover, in a controlled, 6-week study in three adolescents homozygous for the Q188R GALT mutation, adding much larger amounts of galactose to the diet did not significantly change any clinical or biochemical parameters [83]. Endogenous galactose production appears to be greater and much more variable in children vs adults with galactosemia [81], but the influence of this on neurologic outcome is unknown. Taken together, these studies suggest that liberalization of the galactosemia diet with regard to fruits and vegetables is reasonable.

With dietary restriction of dairy products, adequate calcium intake is difficult to achieve without supplements. Low bone density has been reported [84,85], although the long-term complications in terms of bone health are not well characterized.

Effects of Dietary Treatment—Does Strict Dietary Treatment After Early Childhood Improve Adult Outcomes?

Crome observed in 1962 that "it is well known that established mental retardation tends to remain refractory in cases of galactosemia, even after the withdrawal of galactose from the diet, in spite of the reversibility of other signs, e.g. cataracts, hepatic cirrhosis, enteritis, and jaundice" [68], an observation often repeated in ensuing decades [86], and one which raises questions about the value of galactose restriction after early childhood.

Consistent with the notion that strict dietary treatment after early childhood may not be needed, a recent, somewhat controversial case report [87-89] described an adult galactosemic on a normal diet since age 3 years, with only mild cognitive impairment and ovarian failure. This outcome lies within the range of outcomes of patients on life-long galactose restriction. If typical neurologic outcomes may occur despite being untreated with dietary restriction since childhood [87], then the role of galactose restriction after infancy on neurologic outcomes may be less important.

Because dietary galactose restriction has been the standard of care, and is without a doubt lifesaving during early infancy, performing a randomized controlled trial to assess the influence of dietary treatment in early infancy on chronic neurologic outcomes is not possible. A randomized study of graded amounts of galactose in later childhood or adulthood could possibly be safe, but institutional review boards might be unlikely to approve this, and families unlikely to participate in controlled studies where some patients are randomized to not receive standard galactose restriction. However, several alternative quasi-experimental study designs could provide useful information.

One design that could clarify the importance of dietary treatment from birth would be to study sibling pairs, where the first is diagnosed and treated after a period of days to weeks (after newborn screening results are available), and the second child is treated from birth or even prenatally, by restricting the mother's diet.

In one instructive family, with two siblings with mental retardation, tremor, hypotonia, and ataxia, the older, male sibling began galactose-restricted dietary therapy at 17 days old, whereas the female was galactose-restricted from birth [7]. Early developmental milestones were achieved, but cognitive impairments manifested early in both patients. In addition, impaired coordination, tremor, and hypotonia were observed at 5 years old in the older sibling and at 6.5 years in the younger sibling. Diminished signal intensity in the periventricular white matter in both patients and moderate ventricular enlargement in the older sibling were evident on computed tomogram. Neurologic dysfunction, including ataxia, tremor, and dysarthria progressed over the next 8 years, with magnetic resonance imaging demonstrating a small brainstem, cerebellum, an abnormal myelination pattern, and foci of periventricular white matter lesions in both patients [39]. Thus both siblings have a subnormal neurologic outcome, although the older, later treated sibling appeared slightly worse.

A retrospective cohort study looked at effects of early treatment by comparing siblings, where one older sibling was diagnosed after becoming symptomatic (n = 28) and diet began at mean age 63 days, and one or more siblings (n = 31) were diagnosed early and diet was begun at mean age of 1 day [8]. The older sibling's treatment is late by treatment standards in the United States, possibly increasing the chance to identify sibling differences in IQ. IQ measures were stratified into three age groups and compared. At each age level, mean outcomes were 9-15 points higher in the younger-sibling (earlier treatment) group, a clinically beneficial difference. However, the differences were not statistically significant. The authors interpreted these data as failing to provide evidence that early treatment improves outcome.

However, these comparisons of stratified groups of approximately 10 sib-pairs have low statistical power to identify even a fairly large IQ difference. For example, in the 10-16 year age group, there were nine sib pairs. The mean (S.D.) IQ in the probands was 69 (19) and in the younger sibs was 84 (15); reported $P = 0.1$. For these sample sizes and variations, the power to detect a 10-point difference in IQ is less than 20%.

At present, the value of strict or any dietary restriction of galactose after early childhood is unclear. Outside of case reports, short-term dietary studies, and long-term retrospective studies described above, there are no rigorous, prospective, long-term studies to guide decision making. Any changes in standard dietary practices should be accompanied by vigilance for emergence of medical and neurologic complications.

Clinical Trials

There are no well-designed, randomized controlled trials in the treatment of galactosemia. There has been one report of uridine treatment for galactosemia [90]. The authors described a cohort of 35 patients, 29 of whom were given uridine 150 mg/kg/day. The rationales for this investigation were: (1) the observation in hepatocytes and erythrocytes of low levels of UDP-gal in galactosemia patients [91] (this observation has not been consistently reproduced and accepted); (2) the observation that adding glucose + galactose + uridine increased the synthesis in vitro of UDP-gal [91]; and (3) the hypotheses that UDP-gal deficiency might have adverse long-term effects in the central nervous system and that reversing this might be beneficial. The authors explored whether oral uridine could improve neurocognitive performance. Outcomes of interest were results of cognitive tests performed pre- and posttreatment. These revealed small gains which did not distinguish between uridine treated (n = 29) and untreated (n = 6) groups and did not differ by age of treatment onset (7 patients began treatment before 14 months). The authors concluded that the study did not provide evidence of cognitive benefit in their sample of patients.

Limitations of the uridine study include low bioavailability of uridine with no measure of compliance or absorption, nonrandom treatment allocation, significant baseline differences in the measures of the outcome of interest in the treated vs untreated groups, unbalanced treatment arm sizes, and overall low power to detect a meaningful difference.

Summary and Recommendations for Neurologists

Despite advances in the past decade in understanding genetic and molecular aspects of the pathophysiology of galactosemia, many questions remain about the relative contributions of selective neuronal loss and abnormal white matter to the clinical neurologic phenotype. It is likely that neuronal loss and dysmyelination both play a role and occur despite optimal dietary management. Academic neurologists may play a productive role in research collaborations aimed in this area.

Substantial limitations exist in most human-subject research in galactosemia. Most studies exploring the influence of genotype on cognitive phenotype have had low statistical power. Neuroimaging studies have been minimally informative, in part because few quantitative measures have been used. Future studies using functional magnetic resonance imaging and radioactive ligand technology as well as postmortem analyses could provide important general insights into normal and aberrant developmental neurobiology, affecting both gray and white matter. These insights might allow more targeted therapies to emerge.

Most diagnostic testing and treatment decisions for patients with galactosemia will not involve clinical neurologists. However, the subgroup of galactosemic patients that

develops more severe neurologic problems, including ataxia, tremor, and gait disturbance, may be more likely to present to a neurologist's office. Although these symptoms should be recognized as known complications of galactosemia, because genetic and biochemical measures do not predict or explain their emergence, this population may benefit from additional diagnostic testing, mainly magnetic resonance imaging scanning, to exclude other causes. The utility of routine magnetic resonance imaging scanning otherwise is not documented in any recent study. Finally, because there are almost no publications describing symptomatic treatments for these neurologic problems, the clinical neurologist may assist in identifying appropriate medications.

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