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ORIGINAL ARTICLE

The adult galactosemic phenotype

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Abstract
Background Classic galactosemia is an autosomal recessive disorder due to galactose-1-phosphate uridyltransferase (GALT) deficiency. Newborn screening and early treatment do not completely prevent tremor, speech deficits, and diminished IQ in both sexes and premature ovarian insufficiency (POI) in women. Data on how individuals with galactosemia fare as adults will improve our ability to predict disease progression.
Methods Thirty-three adults (mean age=32.6±11.7 years; range=18–59) with classic galactosemia, confirmed by genotype and undetectable GALT enzyme activity, were evaluated. Analyses assessed associations among age, genotype, clinical features and laboratory measures.
Results The sample included 17 men and 16 women. Subjects exhibited cataracts (21%), low bone density (24%), tremor (46%), ataxia (15%), dysarthria (24%), and apraxia of speech (9%). Subjects reported depression (39%) and anxiety (67%). Mean full scale IQ was 88±20, (range=55–122). All subjects followed a dairy-free diet and 75–80% reported low intake of calcium and vitamin D. Mean height, weight and body mass were within established norms. All female subjects had been

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diagnosed with POI. One woman and two men had had children. Logistic regression analyses revealed no associations between age, genotype or gender with IQ, tremor, ataxia, dysarthria, apraxia of speech or anxiety. Each 10- year increment of age was associated with a twofold increase in odds of depression.
Conclusions Taken together, these data do not support the hypothesis that galactosemia is a progressive neurodegenerative disease. However, greater attention to depression, anxiety, and social relationships may relieve the impact of this disorder in adults.

Introduction

Hereditary galactosemia (OMIM 230400; Fridovich-Keil and Walter 2008; Elsas 2010; Berry and Walter 2011) is an autosomal recessive disease due to galactose-1-phosphate uridyltransferase (GALT) deficiency (EC 2.7.7.12), with an incidence of 0.020/1,000 births (1:50,000) in newborn infants in the United States (National Newborn Screening and Genetics Research Center 2009). Classic galactosemia is due to severe GALT gene mutations such as Q188R, K285N and the Ashkenazi Jewish Δ5.2 kb deletion, and is associated with absent or barely detectable GALT enzyme activity in erythrocytes. Untreated patients with classic galactosemia in the newborn period manifest poor feeding, failure to thrive, jaundice, liver disease, cataracts, *E. coli* sepsis, and neonatal death (Berry and Walter 2011). Newborn screening for galactosemia or prompt diagnosis following clinical presentation for galactosemia largely eliminate neonatal deaths through early treatment, including immediate removal of lactose (found in all dairy products and breast milk) and replacement with soy formula.

Yet galactosemia remains a disease that is incompletely treated by diet as evidenced by the common occurrence of central nervous system problems in both sexes (Waggoner et al. 1990) and primary ovarian insufficiency (POI) in women (Kaufman et al. 1981; Rubio-Gozalbo et al. 2010). Neuroimaging studies confirm poor myelination, scattered white matter abnormalities, cerebral atrophy, and cerebellar atrophy in some patients, as well as abnormalities in glucose uptake of metabolism in many brain regions (Dubroff et al. 2008). Patients experience learning disabilities, diminished IQ, executive functioning deficits and speech/ language disorders (Waisbren et al. 1983; Waggoner et al. 1990; Antshel et al. 2004; Potter et al. 2008; Schadewaldt et al. 2010; Shriberg et al. 2011). Some reports raise the specter of progressive cognitive dysfunction (Doyle et al. 2010). Bone turnover may also be impaired (Gajewska et al. 2008).

Despite the evidence for long-term diet-independent effects of galactosemia, there are no comprehensive multidisciplinary evaluations of an adult cohort. Because there are few cross sectional studies of the complete phenotype of affected adults with classic galactosemia at different ages, clinicians, scientists and families cannot predict the adult prognoses for newly diagnosed patients whose lives will be characterized by significant dietary restrictions. To address this gap, we conducted medical, nutritional, genetic, neurological, speech/language, and psychological examinations in 33 adults with classic galactosemia. The research was conducted over one weekend, with all subjects receiving standardized evaluations by one team of investigators. With this method, we could also study how specific issues previously examined in isolation might influence the overall health and well-being of adults with galactosemia. Moreover, we aimed to determine if older adults experienced more symptoms or evidenced greater cognitive dysfunction than younger adults. The hypothesis to be tested was whether classic galactosemia is a progressive disease that includes neurodegeneration.

Methods

Subjects were adults with galactosemia recruited from throughout the United States as self- referral or through the Parents of Galactosemic Children Association. Subjects and their families received scholarships or paid their own ways to participate in the research and attend educational workshops on galactosemia. The Institutional Review Board (Committee on Clinical Investigations) at Children's Hospital Boston approved the study. Informed consent was obtained from each subject. Forty-one researchers and support personnel from Boston, Miami, the state of Washington, and the Netherlands conducted the evaluations or obtained and analyzed laboratory specimens.

Subjects received the following evaluations, described in Table 1: structured physical and neurological examinations, endocrine testing, GALT enzyme assay in erythrocytes and GALT gene sequencing, fertility history, bone density measures, psychological evaluation, speech/language assessment, and nutritional evaluation. In addition, a subset of six subjects received a scalp-electrode based electroencephalogram (EEG) while performing a language production task and a separate subset of eight males agreed to donate semen for analysis.

Descriptive analyses included means and standard deviations for continuous variables, and frequency and percentages for categorical variables. Exploratory analyses using multiple logistic regression analyses assessed associations of outcomes with age and biologic parameters. Data were analyzed using the SAS Statistical System v9.2 (SAS Institute 2010). Unless otherwise noted, all tests were two-sided with significance level 0.05.

Table 1 Methods

Evaluation	Method	# Subjects
Health history	Medical records and interview provided health information.	33
Physical Exam	Physical examination by a physician as well as a neurological examination by an adult neurologist.	33
GALT enzyme	Blood was assessed via a new LC-MS/MS-based assay (Li et al, 2010).	33
GALT gene mutation	Genomic DNA was obtained from subjects for GALT gene sequencing if genotype was not available from medical records.	33
Endocrine and fertility	Blood samples were obtained and evaluated for estradiol, follicle stimulating hormone (FSH), leutinizing hormone (LH), Inhibin B and anti-mullerian hormone (AMH) in women and testosterone, FSH, LH and Inhibin B in men	33
Semen	Semen samples were collected and analyses were made on pH, viscosity, agglutination, red cells, leucocytospermia, motility, VEL , LIN, morphology, percent heads, and percent tails.	8
Reproductive history	Standardized interview and review of medical records provided information on cytorchidism at birth, age at puberty, spontaneous menarche, attempts to conceive, length of time attempted to conceive, number of pregnancies, and number of children.	33
Bone mineral density	Dual-energy x-ray absorptiometry (DXA) scan of hip, neck, and spine.	33
Psychological	Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999), Behavioral Rating Inventory of Executive Functioning-Adult Version (BRIEF-A) (Gioia et al. 2000), Adaptive Behavior Assessment System-Second Edition (ABAS-II) (Harrison and Oakland, 2003), Beck Depression Inventory-Second Edition (BDI-II) (Beck et al. 1996), Beck Anxiety Inventory (BAI) (Beck and Steer 1993)	33
Health quality of life	Interview questions regarding health quality of life, including occupation, education, marital status, and living situation.	13
Speech and language	Tongue strength (Stierwalt and Youmans 2007), Maximum phonation duration (Kent 1994), Goldman-Fristoe Test of Articulation-2 (Goldman and Fristoe 2000), Dysarthria and apraxia of speech (Duffy 2005), Peabody Picture Vocabulary Test-IV (Dunn and Dunn 2007), Hearing	33
Nutrition	Structured interview and 3-day food diary for assessing intake of galactose, calories, calcium and other nutritional parameters. BMI: Underweight=<18.5; Normal weight=18.5-24.9 ; Overweight=25–29.9; Obesity=BMI of 30 or greater.	33
Laboratory	Results from blood samples were compared to reference values for: calcium (Ca), Phosphorous (P), 25-hydroxy vitamin D, Glucose, Glutamic-pyruvate transaminase/alanine amniotransferase (GPT ALT), Alk-Phosphatase, cyclomaltodextrin glucanotransferase (CGT), and Bilirubin (total, direct, and indirect).	33
Electroencephalography (EEG)	Electroencephalography (EEG) recordings were obtained in subjects in conjunction with the performance of a language task to study the brain's reaction to or execution of this task in the form of event related potentials (Luck 2005). A portable electroencephalogram machine was transported from the Netherlands. Electrodes were placed on the head and the recordings were made while subjects completed the task.	6

Results

Subjects (17 males and 16 females; 97% Caucasian) ranged in age from 18 to 59 years (mean age=32.6±11.7 years; median age=31 years). Individual subject results for key variables are presented in Table 2. All subjects received a galactose-restricted diet when they were infants and followed this regimen with varying degrees of rigor through adolescence and into adulthood.

Genotype analyses revealed 15 subjects who were homozygous for the p.Gln188Arg mutation (here referred to as p.Q188R by tradition), 13 with p.Q188R on one allele and a severe mutation, including three deletions, one insertion, and one unclassified mutation, on the other allele. One subject possessed a p.K127Q/deletion genotype and there were three subjects with homozygous deletions. Deletions were noted to be large Δ5.2 kb deletions common in Ashkenazi Jewish individuals (Elsas and Lai 1998; Berry et al. 2001; Goldstein et al. 2011).

Using the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method of Li, (Li et al. 2010) enzyme activity was non-detectable in all subjects, with limit of detectability (LOD) of 0.01 μmol/g Hgb/hour (0.07% of normal control values).

Cataracts in adulthood were noted in medical records or reported during the medical history by 21% of subjects. Nystagmus, irregular pupulatory border, and need for bifocals were noted in 1 subject each. Fifteen subjects (45%) had broken a bone, six during childhood and the others at ages 20 to 46 years. Slight pharyngeal erythema

Table 2 Sample population sorted by age

Sex	Age	GALT gene mutation	Tremor	Ataxia	FSIQ	Depression	Anxiety	Dysarthria	Apraxia of Speech	Children	Low BMD	HT (cm)	BMI kg/m2
Female	18	p.Q188R/p.Q188R	no	No	92	no	yes	no	no	no	yes	161.05	19.4
Female	18	p.Q188R/p.Q344K	postural	No	66	no	yes	yes	no	no	no	176.7	26.9
Female	18	p.Q188R/p.Q188R	no	No	69	no	yes	no	no	no	no	179.8	16.5
Male	20	p.K285N/p.L95P	no	No	107	no	no	no	no	no	no	174.5	19.3
Female	20	p.Q188R/Insertioin (c.70InsA)	no	No	93	yes	yes	yes	yes	no	no	159	22
Male	21	p.Q188R/p.W154X	intention	Yes	122	no	yes	no	no	no	no	175.6	20.3
Male	21	p.Q188R/Deletion	postural	No	83	yes	no	no	no	no	no	180.3	26.4
Male	23	p.Q188R/p.Q188R	no	No	93	no	yes	no	no	no	no	178.1	23.6
Female	23	p.Q188R/p.R259W	no	No	75	no	yes	Not done	Not done	no	no	170.9	20.1
Male	23	p.Q188R/p.R333Y	no	No	112	no	no	no	no	no	no	167.4	20
Male	25	p.Q188R/Deletion	both	Yes	55	no	no	yes	no	no	no	178.3	20.4
Female	25	p.Q188R/Deletion	no	No	79	no	yes	no	no	no	yes	172.5	16.4
Male	25	p.K127Q/Deletion	no	No	112	no	yes	no	no	no	no	169.8	22.6
Male	27	p.Q188R/p.Q188R	no	No	99	no	yes	no	no	no	yes	171.2	20
Female	29	Deletion/Deletion	both	No	106	yes	yes	no	no	no	yes	165.1	22.7
Male	29	p.Q188R/p.K285N	intention	No	55	no	yes	yes	no	no	no	190.5	24.6
Female	31	p.Q188R/ Unclassified mutation	intention	Yes	55	yes	yes	yes	no	no	no	169.6	19.8
Female	31	p.Q188R/p.Q188R	no	No	57	no	no	no	yes	no	no	168.5	20
Male	32	p.Q188R/p.Q188R	postural	No	72	no	yes	no	yes	yes	no	187.8	34.7
Female	32	p.Q188R/p.Q188R	intention	No	88	no	yes	no	no	yes	no	167.4	36.5
Male	33	p.Q188R/p.K285N	intention	No	109	yes	yes	no	no	no	yes	168.5	25
Female	34	p.Q188R/p.Q188R	intention	No	101	no	no	yes	no	no	no	171.6	30.9
Male	34	p.Q188R/p.Q188R	intention	Yes	74	no	yes	yes	no	no	no	176.9	23.6
Female	36	p.Q188R/p.K285N	no	No	96	yes	yes	no	no	no	yes	173.5	29.7
Female	37	p.Q188R/p.Q188R	no	No	97	yes	yes	no	no	no	no	166.05	19.8
Male	45	p.Q188R/p.Q188R	no	No	99	yes	yes	no	no	no	yes	166.9	27.3
Male	45	p.Q188R/p.Q188R	no	No	107	yes	no	no	no	no	no	177.2	22.4
Male	48	p.Q188R/p.N97S	postural	No	66	yes	yes	no	no	no	yes	185	23.5
Female	48	p.Q188R/p.Q188R	no	No	86	no	no	no	no	no	no	150.1	43.1
Female	49	p.Q188R/p.Q188R	no	No	109	yes	yes	no	no	no	no	170.7	28.7
Male	51	p.Q188R/p.Q188R	no	No	107	no	no	no	no	yes	no	172.4	25.5
Female	55	Deletion/Deletion	postural	No	108	yes	no	no	no	no	no	155.7	27.7
Male	59	Deletion/Deletion	no	Yes	67	yes	no	yes	no	no	no	172.6	22

FSIQ=Full scale IQ derived from Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999)

Depression: Score greater than 13 on the Beck Depression Inventory, Second Edition (BDI-II) (Beck et al 1996)

Anxiety: Score greater than 7 on Beck Anxiety Inventory (BAI) (Beck and Steer 1993)

Low BMD=Low bone mineral density, defined as z-scores greater than 2 standard deviations below the normative mean (Kelly 1990; Looker et al. 1995)

was noted in two subjects. Other medical issues, each noted in only one subject, included joint pain, musculoskeletal scoliosis, kidney stone, adult onset seizures, poor dental condition, café au lait spots, systolic heart murmur, high blood pressure, and mitral valve replacement.

Tremor was noted in 15 subjects (46%), with intention tremor in eight (24%), postural tremor in five (15%), and both kinds of tremors in two (6%) subjects. Ataxia was noted in five subjects (15%) and two subjects (6%) manifested dystonia. Two subjects were left handed (6%).

Full scale intelligence quotient (FSIQ) derived from the Wechsler Abbreviated Scales of Intelligence (Wechsler 1999) ranged from 55–122, with a mean of 88±20. Thirteen subjects (39%) attained scores ≤85, with eight (24%) of these subjects attaining scores ≤70 (indicating intellectual disability). Scores on the verbal (vocabulary) and nonverbal (matrix reasoning) subtests did not differ, with means of 42 ±15 for vocabulary and 42±14 for matrix reasoning (normal mean=50). Deficits in executive functioning, as indicated by scores above 65 on the Behavior Rating Inventory of Executive Function (Gioia et al. 2000) were noted in 5 (15%) subjects. Seven (21%) subjects attained scores less than 85 on the Adaptive Behavior Assessment System. (Harrison and Oakland 2003). Fifteen subjects (46%) lived independently, including nine who were either married or living with partners. Average schooling was 1–2 years of college. Seven subjects (21%) were unemployed (and not in school). The typical occupational level was that of skilled manual laborer.

At the time of the study visit, depression, characterized by scores greater than 13 on the Beck Depression Inventory (Beck et al. 1996) was present in four individuals (12%), two of whom were being treated with anti-depressant medication. Six subjects reported having received anti-depressant medication at some point in their lives, including a young man who received electro-convulsive therapy. Three additional subjects reported suffering from depression in the past, raising the total number of subjects with observed or reported depression to 13 (39%) compared to 16.2% lifetime prevalence in the general adult population in the US (Kessler et al. 2003). Anxiety, indicated by scores greater than seven on the Beck Anxiety Inventory, (Beck and Steer 1993) was reported by 17 subjects (52%) (three were taking medication for anxiety) compared to 16.4% yearly prevalence of anxiety in the general adult population in the US (Surgeon General 2009). Five additional subjects had received medication for anxiety in the past, raising the total number of subjects with a history of anxiety to 22 (67%).

The majority of subjects exhibited deficits in motor speech function as defined by scores of 1 standard deviation or more below the mean of healthy controls on standardized measures. Reduced tongue strength, as measured by the Iowa Oral Performance Instrument (Stierwalt and Youmans 2007), was noted in 24 (73%) subjects. Breath support for speech, as measured by decreased phonation duration (Kent 1994), was decreased in 21 (64%) subjects, and articulation proficiency (Goldman and Fristoe 2000) was reduced in four (12%) subjects. Dysarthria, a sensorimotor speech disorder due to weakness, incoordination, involuntary movements, or abnormal muscle tone (Duffy 2005), was observed in eight subjects (24%). Apraxia of speech, affecting the planning and programming of speech movements (Duffy 2005), was noted in three subjects (9%). Receptive vocabulary (Dunn and Dunn 2007) was reduced in 14 (42%) subjects. Three men (and no women) had mild-moderate high frequency hearing loss (two unilateral; one bilateral). Preliminary analyses of event-related potentials (ERPs) derived from the continuous EEG (Luck 2005) in a subset of subjects, showed a deviant pattern compared to healthy adults in terms of the brain's reaction to a language task. Error and voice onset data revealed a difference ($p<.001$) between the six subjects and a normative sample (errors: 20.8% vs. 6.4%; voice onset latency: 5.5 seconds vs. 1.5 seconds, respectively).

All female subjects had previously been diagnosed with POI. Consistent with that diagnosis was the finding of reduced serum AMH levels well below 0.3 ng/ml (mean=0.025±0.022 ng/ml; range=0.01-0.07 ng/ml). Additional endocrine studies also indicated ovarian insufficiency in females not receiving estrogen replacement therapy. Estradiol in females ranged from 10 pg/mL to 129 pg/mL (mean=33±36; reference range=21–649 pg/mL). FSH in female subjects ranged from 0.14-109.44 (mean=32.77±32.99; reference range=1.38-16.69 mlU per mL). Eleven women experienced spontaneous menarche. The average age of menarche was 15.1± 1.8 years for women, including those receiving hormonal treatments to induce menstruation. In men, average age of self-reported puberty was 13.7±1.8. Average age of puberty in the general population is currently about 13 years for girls and 14 years for boys (http://www.mgh.harvard.edu/children/ adolescenthealth/articles/aa_puberty.aspx). In male subjects, FSH ranged from 1.31-8.49 mlU per mL (mean= 4.33±2.6; reference range=.95-11.95 mlU per mL). Testicular abnormalities (cryptorchidism) had occurred in one male at birth. Testicular size was within normal range (mean= 28 ±4.06 cc, range=25–35 cc). Of the eight men who provided a semen sample, one had a low sperm count and two had low percent normal morphology. Among the 12 male and 10 female subjects who responded to the question about sex, five (42%) men and seven (70%) women reported having had intercourse. Three women in the total sample tried to conceive without achieving pregnancy. One woman became pregnant after trying for 60 months and gave birth to a healthy child. Two men were fathers, with one child each.

Table 3 Results of logistic regression analyses to assess the association of genotype, gender, and age with several study outcomes. Individual fixed effects are reported as odds ratios (ORs) with 95% confidence interval and p-value. Overall model significance was determined using the likelihood ratio test

	Age (10 yr increase)	Gender (male vs. female)	Genotype (deletion/ no deletion)	Overall model significance
IQ<85	0.75 (0.39, 1.41) p=0.37	1.17 (0.27, 4.96) p=0.83	2.73 (0.47,15.82) p=0.26	0.57
Depression	2.98 (1.23, 7.17) p=0.02	0.51 (0.10, 2.70) p=0.43	3.45 (0.42, 28.55) p=0.25	p=0.02
Anxiety	0.53 (0.10, 1.12) p=0.25	0.48 (0.09, 2.43) p=0.37	0.27 (0.04,1.75) p=0.17	p=0.11
Tremor	0.88 (0.47, 1.63) p=0.68	1.47 (0.36, 6.04) p=0.59	2.16 (0.39,12.07) p=0.38	p=0.75
Ataxia	1.11 (0.49, 2.49) p=0.81	4.55 (0.43, 47.58) p=0.21	2.97 (0.36,24.75) p=0.31	p=0.38
Apraxia of speech	0.62 (0.17, 2.30) p=0.48	0.45 (0.03, 5.97) p=0.55	- - - -	p=0.46
Dysarthria	0.87 (0.43, 1.77) p=0.70	0.85 (0.17, 4.23) p=0.84	1.31 (0.20,8.70) p=0.78	p=0.97
Had child	1.90 (0.57, 6.34) p=0.29	1.89 (0.14, 25.47) p=0.63	——	p=0.38

Bone density was, on average, greater than a standard deviation below the normal mean (z=−1.1) (Kelly, 1990; Looker et al. 1995). A total of eight subjects (24%) had a z score greater than 2 standard deviations below the mean on bone mineral density measurements.

Nutritional evaluations indicated that all subjects reported following a lactose-restricted or dairy-free diet with avoidance of milk and milk products. Forty-one percent of subjects referred to written diet guidelines, but the majority (90%) no longer received nutritional counseling. Two-thirds of subjects took calcium supplements and 38% took vitamin D supplements, but did so irregularly. Dietary records showed an average intake (without supplementation) of 675 mg calcium, 3.8 mcg vitamin D, 1110 mg phosphorus, and 282 mg magnesium. Eighty percent of subjects had intakes below the daily recommended intake (DRI) for calcium and 75% had intakes below the DRI for vitamin D. Mean plasma 25-hydroxy vitamin D level was 27±11 ng/ml (reference range 32–100 ng/ml), with 80% of subjects below the sufficient range (Stoffman and Gordon 2009). Average height was 167.39±7.77 cm for females (US 50th% for women=165.5 cm) and 176.06±6.90 cm for

Table 4 Genotype and frequency of IQ ≤85, and presence of tremor, dysarthria/dyspraxia, depression, and anxiety

Genotype (n)	IQ	Tremor	Dysarthria or apraxia	Depression (BDI>13)*	Anxiety (BAI>7)**
p.Q188R/p.Q188R (15)	57-109	27%	27%	27%	20%
p.Q188R/Unclassified (1)	55	yes	yes	No	yes
p.Q188R/p.W154X (1)	122	yes	no	No	no
p.Q188R/Deletion (3)	55,79, 83	67%	33%	33%	33%
p.Q188R/p.R259W (1)	75	no	-	No	no
p.Q188R/p.N97S (1)	66	yes	no	No	yes
p.Q188R/p.K285N (3)	55,96,109	67%	33%	67%	67%
p.Q188R/p.R333Y (1)	112	no	no	No	no
p.Q188R/p.Q344K (1)	66	yes	yes	Yes	yes
p.Q188R/Insertion (c.70InsA) (1)	93	no	yes	No	no
K285N/p.L95P (1)	107	no	no	No	no
K127Q/Deletion (1)	112	no	no	No	no
Deletion/Deletion (3)	55,79,83	67%	33%	33%	33%

*BDI=Beck depression inventory

*BAI=Beck anxiety inventory

males (US 50th% for men=179 cm) (Center for Disease Control and Prevention 2000). Body mass index results indicated that the majority of subjects (58%) maintained weights within the normal range for height and sex. Two women (13%) were underweight, four (25%) were overweight and two (13%) were obese. Among male subjects, four (24%) were overweight and one (6%) was obese.

Bilirubin (direct) was normal in all subjects and the mean bilirubin indirect was well within the average range (0.39± 0.28 mg/dl, range=0.12-1.06 mg/dl; reference range=0.1-0.8 mg/dl).

Logistic regression analyses revealed few significant associations between potential predictors and outcomes (Table 3). Age was not related to IQ, anxiety, tremor, ataxia, dysarthria, apraxia of speech, or whether or not the subject had a child. Each 10- year increment of age was associated with a 3-fold increase in odds of depression at some point in life. However, age was not associated with scores on the Beck Depression Inventory measuring depressive symptoms at the time of the study (r=0.14, 95% CI (−0.22, 0.46), p=0.56). Older individuals exhibited a higher body mass index (r=0.41, 95% CI (0.08, 0.66), p=0.02).

Males and females exhibited similar rates of anxiety, depression, speech deficits and neurological signs and did not differ in terms of IQ or becoming parents.

Whether or not a subject had a Δ5.2 kb deletion on one or more alleles was not predictive of any examined outcome (Table 4). The percentage of subjects with tremor, ataxia, or speech defects was not associated with genotype. Subjects homozygous for the common p.Q188R genotype experienced a similar range of scores on IQ tests and measures of depression and anxiety as subjects with deletions or unclassified mutations on one allele.

Discussion

This study documents the occurrence of tremor, nutritional deficits, reduced bone density, diminished cognitive functioning, speech abnormalities, depression, and anxiety in association with galactosemia in adulthood. There were women experiencing primary ovarian insufficiency and many men who did not engage in sexual relationships. Also included in this sample were college students and teachers, and individuals in successful marriages. What may be most significant and what has not been described before is that symptoms did not go hand-in-hand. For example, individuals with tremor did not necessarily exhibit diminished cognitive functioning. Those with speech deficits were not necessarily depressed or anxious. A second significant finding was that older subjects compared to younger subjects did not exhibit poorer physical or mental health or a lower level of cognitive functioning. Thirdly, the predominance of dysarthria with vocal characteristics indicative of cerebellar dysfunction suggests central nervous system involvement of the cerebellum and its relative circuitry. The timing of this injury to the central nervous system needs to be established. Finally, genotypes, predominantly p.Q188R alleles, were uninformative in predicting examined outcomes in patients with zero residual GALT enzyme activity. Other studies described similarly variable outcomes in subjects with classic galactosemia associated with severe GALT mutations (Shield et al. 2000).

Possibly, genotype had an indirect effect on health and quality of life outcomes in our sample. For example, few men in our study had experienced sexual relations and even fewer tried to become fathers. Perhaps they were overly reserved or delayed in their psychosexual development, as has been suggested by Bosch et al. (2004). Or perhaps, expressive language difficulties may have interfered with their ability to initiate that first overture or sustain conversations with a date. Whether anxiety and depression, common among adults of either sex in this sample, resulted from hormonal variations associated with galactosemia or reflected discouragement and worry over infertility or cognitive, speech and motor challenges is not yet known.

Our study was limited due to sample size and the accrual process through the parent organization. There was an absence in this study of less severe mutant alleles such as the S135L seen predominantly in patients with African ancestry. Comparisons between individuals with mild and severe genotypes may be worthwhile in future studies.

The results of our study indicate a need to address psychosocial as well as medical issues when treating individuals with galactosemia. Greater attention to depression, anxiety, and social relationships may do much to relieve the impact of this disorder in adults.

Prospective studies that include individuals identified by newborn screening as well as individuals identified because of clinical signs are needed to assess the development and progression of symptoms over time. While it is tempting to focus on genotype-phenotype relationships in galactosemia, future studies need to take a broader perspective that includes interrelationships among the genetic (including whole genomic modifiers), epigenetic, and environmental factors that influence long-term outcomes in this disorder. Lastly, taken together, the data do not support the hypothesis that galactosemia is a progressive neurodegenerative disease.

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