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RESEARCH REPORT

Motor and Speech Disorders in Classic Galactosemia

Nancy L. Potter • Yves Nievergelt • Lawrence D. Shriberg

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Abstract ***Purpose*** To test the hypothesis that children with classic galactosemia and speech disorders are at risk for co-occurring strength and coordination disorders.

Method This is a case–control study of 32 children (66% male) with galactosemia and neurologic speech disorders and 130 controls (50% male) ages 4–16 years. Speech was assessed using the Percentage of Consonants Correct (PCC) metric from responses to the Goldman-Fristoe Test of Articulation-2 and from a 5-min recorded speech sample, hand and tongue strength using the Iowa Oral Performance Instrument, and coordination using the Movement Assessment Battery for Children. The number of days on milk during the neonatal period was obtained by parent report. Analyses of covariance, distributions, and correlations were used to evaluate relationships among speech, strength, coordination, age, gender, and days on milk.

Results Children with galactosemia had weaker hand and tongue strength and most (66%) had significant coordination disorders, primarily affecting balance and manual dexterity. Among children with galactosemia, children with more speech errors and classified as childhood apraxia of speech ($n = 7$) and ataxic dysarthria ($n = 1$), had poorer balance and manual dexterity, but not weaker hand or tongue strength, compared to the children with fewer speech errors. The number of days on milk during the neonatal period was associated with more speech errors in males but not in females.

Conclusion Children with galactosemia have a high prevalence of co-occurring speech, coordination, and strength disorders, which may be evidence of a common underlying etiology, likely associated with diffuse cerebellar damage, rather than distinct disorders.

Abbreviations

CAS	Childhood Apraxia of Speech
kstest	Kolmogorov-Smirnov one sample one-tail test statistic
kstest2	Kolmogorov-Smirnov two sample one-tail test statistic
MABC	Movement Assessment Battery for Children
MSD-NOS	Motor Speech Disorder-Not Otherwise Specified
PCC:AT	Percentage of Consonants Correct from an Articulation Test
PCC:CS	Percentage of Consonants Correct from a 5-minute Conversational Speech Sample

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N.L. Potter (✉)
Department of Speech and Hearing Sciences, Washington State University Spokane, 412 E. Spokane Falls Blvd.,
Spokane, WA 99202-2131, USA
e-mail: nlpotter@wsu.edu

Y. Nievergelt
Department of Mathematics, Eastern Washington University, Cheney, WA 99004, USA

L.D. Shriberg
Waisman Center, University of Wisconsin-Madison, Madison, WI 53706, USA

Classic galactosemia (OMIM 230400; referred to as galactosemia in this article) is a rare recessive autosomal inborn error of metabolism that prevents individuals from metabolizing galactose, a sugar present in breast milk and milk-based formula (Berry and Elsas 2011). During the newborn period, galactosemia may affect multiple organs and can be life threatening in infants ingesting lactose in

breast milk and milk-based formulas. In the United States, galactosemia is diagnosed through newborn screening with an incidence of 1 in 40,000–60,000. With early diagnosis and dietary galactose restriction through the elimination of breast milk or milk-based formula, children survive but are at risk for long-term complications including language (90 %), speech (60 %), cognitive (50 %), motor disorders (18 %; Waggoner et al. 1990), and gonadal failure in females (>80–90 %; Fridovich-Keil et al. 2011). Most studies report that the severity of long-term complications has minimal or no association with the number of days milk is consumed during the neonatal period prior to the galactosemia diagnosis (Berry and Elsas 2011).

Speech disorders in children with galactosemia, which have a neurologic origin, are classified as one of the following three subtypes of motor speech disorders: (1) childhood apraxia of speech (CAS), a deficit in motor planning or programming, (2) dysarthria, a deficit in neuromuscular control, or (3) motor speech disorder-not otherwise specified (MSD-NOS), a cover term for speech, prosody, and voice behaviors that are consistent with a motor speech disorder, but not specific for CAS or dysarthria (Shriberg et al. 2011).

Children with galactosemia and speech disorders have a high co-occurrence of motor disorders (Waggoner et al. 1990). Motor disorders include deficits in strength and coordination (Gaines and Missiuna 2007; Gallup et al. 2007; Pieters et al. 2012; Raynor 2001). Speech and coordination disorders frequently co-occur in the general population (Gaines and Missiuna 2007; Pieters et al. 2012). In a recent study of more than 3,000 children referred for an assessment of developmental delays, one-third (33.7 %) of children with speech disorders had co-occurring coordination disorders as opposed to <10 % in the general population (Pieters et al. 2012). Investigators have proposed that co-occurring coordination and speech disorders should not be considered two distinct disorders but rather the result of a common underlying etiology affecting a number of motor domains including speech (Gaines and Missiuna 2007; Pieters et al. 2012). Males are at greater risk for developmental disorders, with approximately twice the prevalence of coordination (1.8:1) and speech disorders (2:1) compared to females (Pieters et al. 2012). While speech disorders have been reported to affect 60 % of children with galactosemia (Waggoner et al. 1990), the ratio of males to females with speech or coordination disorders in galactosemia is not known.

Motor disorders have been reported in children with galactosemia (Waggoner et al. 1990) but the term "motor" has not been defined nor have the components of motor disorders been systematically assessed. The present study examined strength and coordination, two components of motor development that contribute to a motor disorder (Pieters et al. 2012; Raynor 2001) and their relationships to measures of speech production. Males and females were analyzed separately as males are more at risk for developmental disorders (Raynor 2001). Days on milk during the neonatal period was included in the analyses as the possibility of an association has not been definitively ruled out (Waggoner et al. 1990). Thus, the objectives of the present study were to: (1) determine if children with galactosemia and speech disorders differ from controls in strength and coordination skills, (2) examine relationships among speech, strength, and coordination skills, and (3) ascertain if there are relationships among the severity of motor or speech disorders and early ingestion of milk in children with galactosemia.

Methods

A total of 163 children between 4 and 16 years of age participated in this case–control study, which was part of a larger study of CAS (Potter et al. 2008; Potter 2011; Shriberg et al. 2011). There were 32 children with galactosemia, 21 males and 11 females, and 130 control children, 5 males and 5 females from each 6-month age group from 4–16 years of age (Potter et al. 2012). Children with galactosemia met the following criteria: (a) a confirmed diagnosis of classic galactosemia, (b) a history of treatment for speech disorders, (c) English as a first language, (d) no significant hearing loss as measured by a pure tone screening test, and (e) no craniofacial anomalies. Half (49 %) of the children with galactosemia had IQs in the normal range (85–115), 39 % in the borderline range (70–84), and 12 % in the low range (below 70; Potter et al. 2008). One male with galactosemia was assessed but excluded from the present study because of a diagnosis of cerebral palsy and an inability to complete the motor assessment. Controls met the following criteria: (a) academic performance at grade level with no history of referral for special educational services, (b) articulation within normal limits on a standardized articulation test, (c) English as a first language, (d) hearing within normal limits on a pure tone screening test, and (e) no craniofacial anomalies. Normal cognitive development in the controls was documented by teacher and parent questionnaire, with both groups indicating that the participant was functioning at or above grade level in academic subjects and physical education and had never been referred for special education.

The children with galactosemia were recruited through website, e-mail, and postal announcements to two support groups, Galactosemia Foundation and Galactosemic Families of Minnesota, and to metabolic clinics across the United States. All children with galactosemia were tested in their homes in 17 different states across the United States. Parents completed a written health history form. As reported by parents, all children with galactosemia adhered to a lactose-restricted diet. The control

participants were recruited from and tested at preschools and public schools in Washington State. A speech-language pathologist with advanced training in kinesiology tested all the participants.

The Madison Speech Assessment Protocol and the Speech Disorders Classification System (Shriberg et al. 2010) was used to classify speech as typically developing (all controls) or as meeting the criteria for one of the three motor speech disorder subtypes (all participants with galactosemia): (1) CAS ($n = 7$), (2) ataxic dysarthria ($n = 1$, referred to as dysarthria in this paper), and (3) MSD-NOS ($n = 24$; Shriberg et al. 2011). Speech findings were obtained by phonetically transcribing the children's responses to the Goldman-Fristoe Test of Articulation-2 (PCC:AT; Goldman and Fristoe 2000) and from a 5-min conversational speech sample (PCC:CS) and dividing the number of consonants produced correctly by the total number of consonants to obtain the *percentage of consonants correct* (PCC).

Tongue and hand strength were assessed using the Iowa Oral Performance Instrument (IOPI) with the standard silicon tongue bulb and the air-and-silicone-filled hand bulb. To measure tongue strength, the tongue bulb was positioned on the participant's alveolar ridge, immediately posterior to the central incisors (IOPI Northwest 2005). The children were asked to raise their tongues and squeeze the bulb against the palate as hard as they could for 2–3 s. To measure dominant and nondominant hand strength, the hand bulb was positioned in the center of the children's palms. The participants were asked to curl their fingers around the bulb and squeeze as hard as they could for 2–3 s. For each strength measurement, the children performed three trials with a 30-s rest between trials. The highest value from the three trials was defined as maximum strength. Ninety-one percent of the children with galactosemia, including all the children with CAS or dysarthria, and 85 % of the controls were right hand dominant.

Coordination in the children with galactosemia was assessed using the Movement Assessment Battery for Children (MABC) with scores compared to the published norms (Henderson and Sugden 1992). The MABC has three subtests, manual dexterity, ball skills, and balance, and a total impairment score, which is a sum of the three subtests. Higher scores indicate greater impairment. The first edition of the MABC, used in the present study, included reference data for participants ages 4–12 years. The comparative data for age 12 years was used for children ages 13–16 ($n = 3$).

The above assessments were conducted among children with galactosemia in their homes using a protocol that included measures in addition to those discussed in the present study (Potter et al. 2008; Potter 2011; Shriberg et al. 2011). Controls were assessed in a quiet schoolroom during the school day.

The Institutional Review Boards of the University of Wisconsin-Madison and Washington State University approved this study. A parent of each participant provided written consent, children age 12 years and older provided written consent, and children 11 years and younger provided written or verbal informed assent.

Statistical Analysis

Normality tests (Lilliefors and Jarque-Bera; MATLAB 2012) were done on all variables and residuals from their ordinary least-squares regressions on age, for all groups and subgroups. Statistically significant differences from two-sample one-tail *t*-tests, analyses of variance or analyses of covariance are reported for variables or residuals that passed at least one normality test in each group or subgroup. One-sample or two-sample, one-tail Kolmogorov-Smirnov tests (*kstest* or *kstest2*) were also performed on all variables, groups, and subgroups and statistically significant differences reported. Within groups, pairs of variables were subjected to tests of Pearson's and Spearman's correlation coefficients (with partial correlations to adjust for age). An $\alpha = 0.05$ was used for all analyses.

Results

Genders were combined where relationships among variables did not differ by gender (comparison between controls and galactosemia on the speech measures PCC:AT and PCC:CS) or no information was available by gender (MABC subtest and total scores). Analyses were done separately by gender for all other variables.

Speech

Males and females with galactosemia had more articulation errors (fewer consonants correct) than the controls on the articulation test and during conversation (PCC:AT, $kstest2 = 0.70$, $P = 2.93 \times 10^{-12}$ and PCC:CS, $kstest2 = 0.73$, $P = 2.69 \times 10^{-13}$). Within the galactosemia group, the children diagnosed with CAS or dysarthria had more speech errors on the articulation test and during conversation (PCC:AT, $kstest2 = 0.58$, $P = 0.0095$ and PCC:CS, $kstest2 = 0.58$, $P = 0.0095$) compared to the children classified as MSD-NOS.

Strength

As shown in Fig. 1, males with galactosemia had weaker tongue strength compared to the control males ($kstest2 = 0.7355$, $P = 9.52 \times 10^{-9}$) and females with galactosemia had weaker tongue strength compared to the control females ($kstest2 = 0.8615$, $P = 2.01 \times 10^{-7}$).

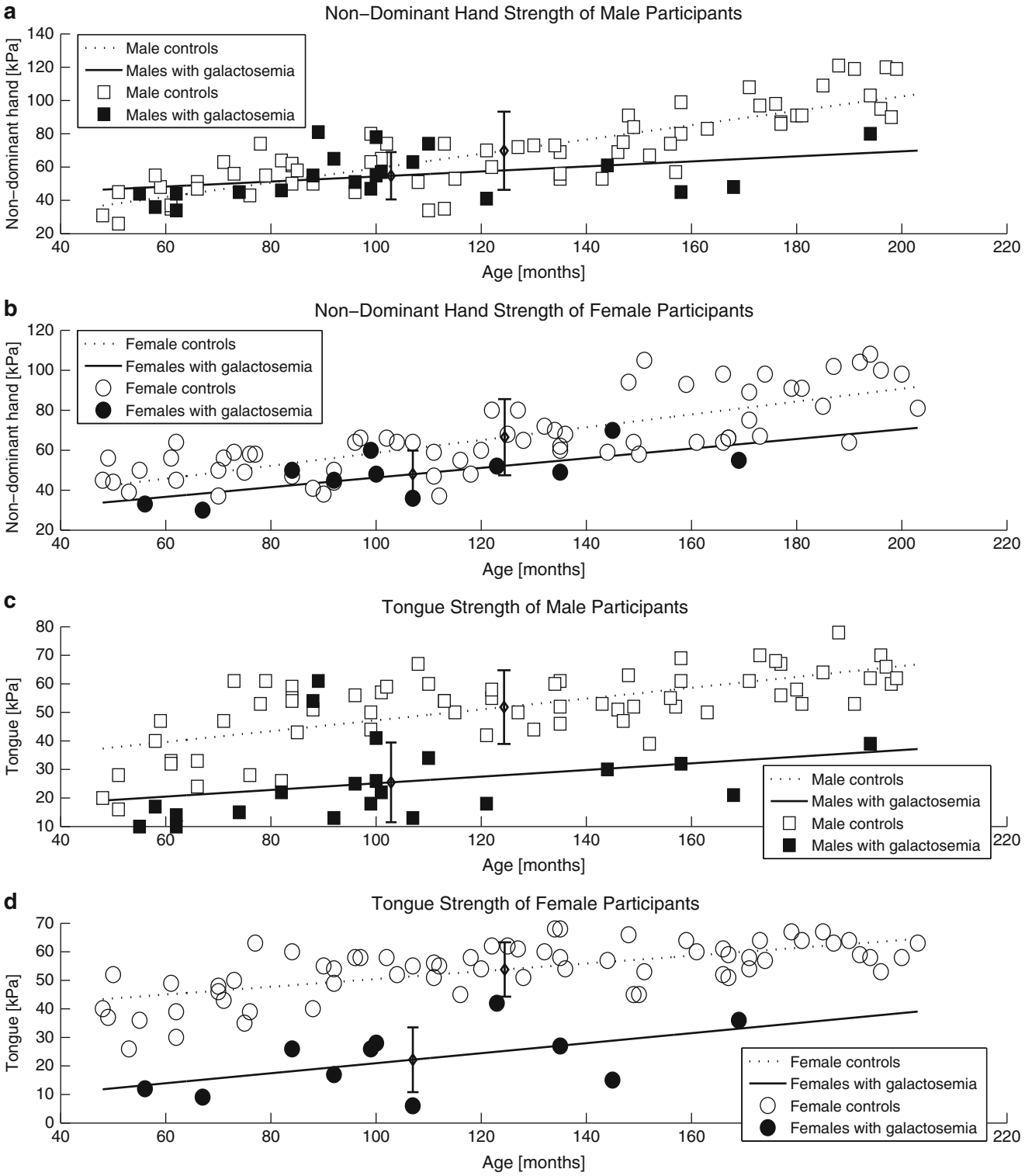

Fig. 1 Nondominant and dominant hand strength as a function of age. Means and standard deviations shown by diamonds and whiskers

Within the galactosemia group, tongue strength was equivalent across diagnoses (CAS, dysarthria, and MSD-NOS) and genders.

Comparison across groups showed that males with galactosemia had weaker dominant and nondominant hand strength (lower means for dominant hand, $t = 3.20$,

$P = 0.0012$ and nondominant hand, $t = 3.53$, $P = 4.09 \times 10^{-4}$). However, at the younger ages, males with galactosemia had greater hand strength (larger intercepts for dominant hand, $t = 2.76$, $P = 0.0072$ and nondominant hand, $t = 2.34$, $P = 0.022$) but then increased at a slower rate (shallower slopes for dominant hand, $t = 3.61$, $P = 5.32$ x 10^{-4} and nondominant hand, $t = 3.22$, $P = 0.0018$) compared to the male controls.

Females with galactosemia also had weaker dominant and nondominant hand strength (lower means for dominant, $t = 3.80$, $P = 6.04 \times 10^{-4}$ and nondominant hand, $t = 4.32$, $P = 1.64 \times 10^{-4}$). Unlike the males at the younger ages, they had weaker dominant and nondominant hand strength (smaller intercepts) and remained weaker across age (equivalent slopes) compared to the female controls. Within the galactosemia group, children with apraxia or dysarthria had equivalent hand strength compared to children with MSD-NOS.

Dominant hand strength was 2 % greater for male controls, 4 % greater for female controls, 0.3 % greater for males with galactosemia, and 4 % greater for females with galactosemia than nondominant hand strength, but these differences were not statistically significant. In the general population, there is no difference in hand strength in left-hand-dominant individuals. Dominant hand strength may be up to 10 % stronger in right-hand-dominant individuals (Gallup et al. 2007; Häger-Ross and Rösblad 2002).

Coordination

The performances of the children with galactosemia on the MABC were compared to the general population norms published in the test manual (Fig. 3; Henderson and Sugden 1992, p. 109), which are partitioned into two mutually disjoint age groups: "Ages 4 and 5 years" and "ages 6 and above". For comparison, the scores of the children in the present study were partitioned into the corresponding age groups, with 4 males and 2 females under 6 years of age, and 17 males and 9 females age 6 years and above. Typical tests of whether a sample was drawn randomly from a general population use the population cumulative distribution function (CDF), not percentiles as provided in the MABC test manual. Therefore to compare each age group of participants with the corresponding age group from the general population, the percentiles for each age group were converted into a by the formula: $\text{CDF} = \frac{\text{100-percentile}}{100}$. As shown in Fig. 2, a one-tailed, one sample Kolmogorov-Smirnov test (computed with MATLAB's *kstest*; MATLAB 2012) showed that the combined scores for coordination skills, as measured by the MABC total score, of the 4- and 5-year-old children with galactosemia were markedly below that of the general population (ksstat = 0.84, $P = 1.68 \times 10^{-5}$) as were the coordination skills of the children 6 years and older (ksstat = 0.66308, $P = 4.56 \times 10^{-12}$).

Fifty-three percent (17/32) of the children with galactosemia and speech disorders scored at or below the 5th percentile and 66 % (21/32) scored below the 10th percentile on the total score of the MABC, which are two of the frequently used cutoff scores for a coordination disorder diagnosis (Gaines and Missiuna 2007; Pieters et al. 2012). Using the MABC total impairment score, children with galactosemia and speech disorders have increased odds of 3.5 (odds ratio) of a co-occurring coordination disorder as compared to the general population with speech and language disorders (Pieters et al. 2012). Subtest scores (for manual dexterity, ball skills, and balance) could not be compared, as data for the general population was not published in the MABC manual or in subsequent publications. As shown in Fig. 3, the children with galactosemia who were diagnosed with CAS or dysarthria had poorer manual dexterity ($F = 4.55$, $P = 0.04$), markedly poorer balance ($F = 23.20$, $P = 4.0 \times 10^{-5}$), and poorer total scores ($F = 11.62$, $P = 0.0019$) on the MABC compared to the children diagnosed with MSD-NOS.

As shown in Table 1, poor coordination, measured by balance, ball skills, manual dexterity, and the total score on the MABC, was associated with weak dominant and nondominant hand and tongue strength in males, but not in females, with galactosemia. With genders collapsed, poor balance and manual dexterity were associated with weak tongue strength but not hand strength in children with galactosemia and MSD-NOS. Coordination was not associated with strength in children with galactosemia and CAS or dysarthria.

Days on Milk

The number of days on milk was associated with poorer articulation (PCC:AT, $\rho = -0.49$, $P = 0.03$; PCC:CS, $\rho = -0.45$, $P = 0.045$) for males with galactosemia but not for females with galactosemia ($P = 0.06$). The number of days on milk was not associated with measures of strength (range for $P = 0.78 - 0.82$) or coordination (range for $P = 0.26 - 0.63$).

Discussion

This is the first study to examine relationships among motor speech, strength, and coordination disorders in any pediatric population. It is also the first study to relate motor skills to speech disorders by gender in children with galactosemia. Compared to the controls, (1) males and females with galactosemia had weaker tongue strength across ages, (2) females with galactosemia had weaker hand strength

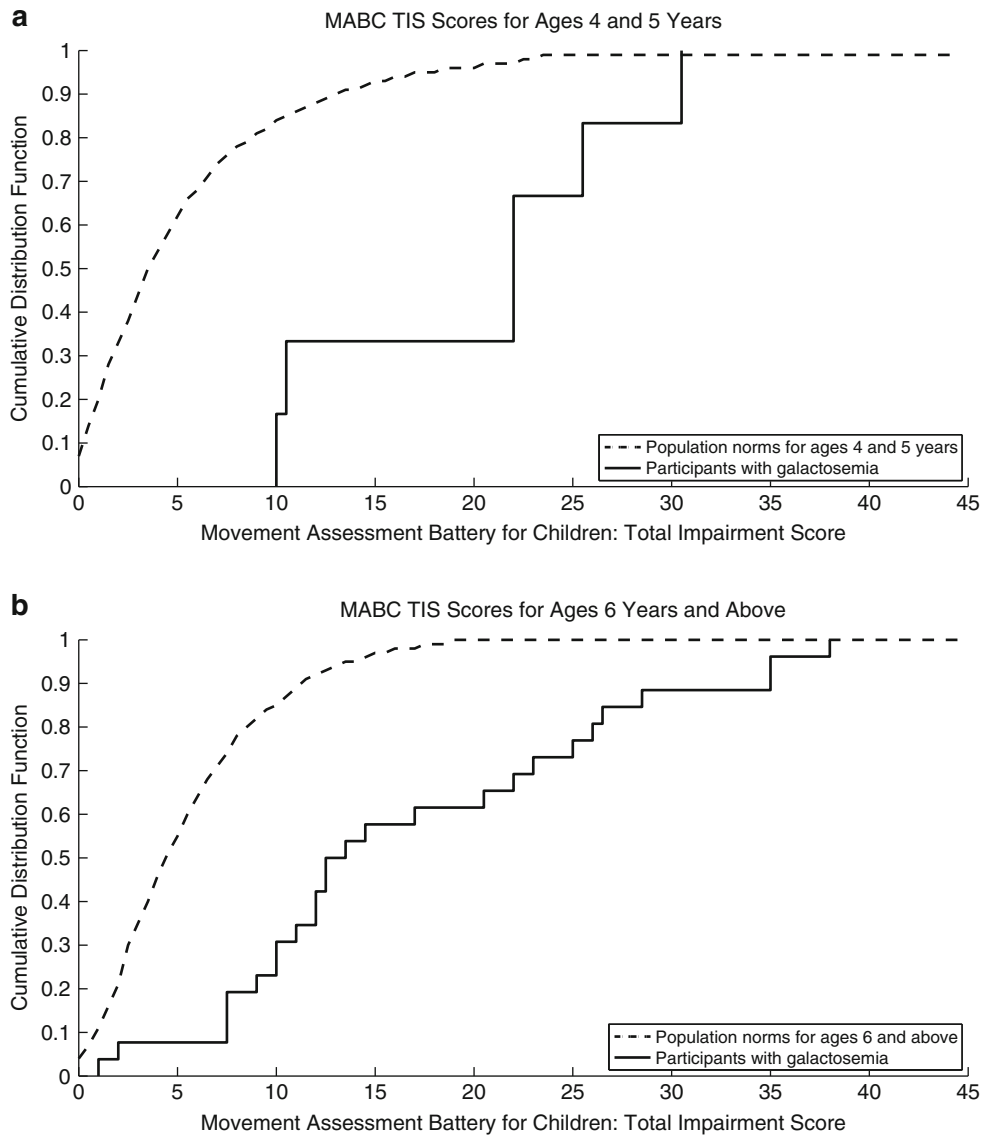

Fig. 2 Cumulative distribution functions of the MABC total impairment scores. Greater MABC total impairment scores correspond to greater impairment

across ages, (3) males with galactosemia had equivalent or slightly stronger hand strength at the younger ages but did not show the typical increase in hand strength expected of males during adolescence, (4) 66 % of children with galactosemia and speech disorders had co-occurring coordination disorders, (5) children with galactosemia and CAS or dysarthria had poorer balance and manual dexterity, and (6) the number of days on milk during the neonatal period was associated with worse speech outcomes for males, but not females, with galactosemia.

Speech

All children with galactosemia showed evidence of a neurological origin for their speech disorder, which was classified as one of the three subtypes of motor speech disorders: (1) CAS, (2) dysarthria, and (3) MSD-NOS (Shriberg et al. 2011). The children with CAS or dysarthria exhibited more speech errors and were less intelligible than the children with MSD-NOS.

Strength

We predicted that tongue strength would be reduced in males and females with galactosemia and speech disorders based on the results of two small-scale studies that examined tongue strength in CAS. Together these studies reported that eight of 10 children (nine males and one female) with CAS had weaker tongue strength compared to controls, suggesting that weak tongue strength may be

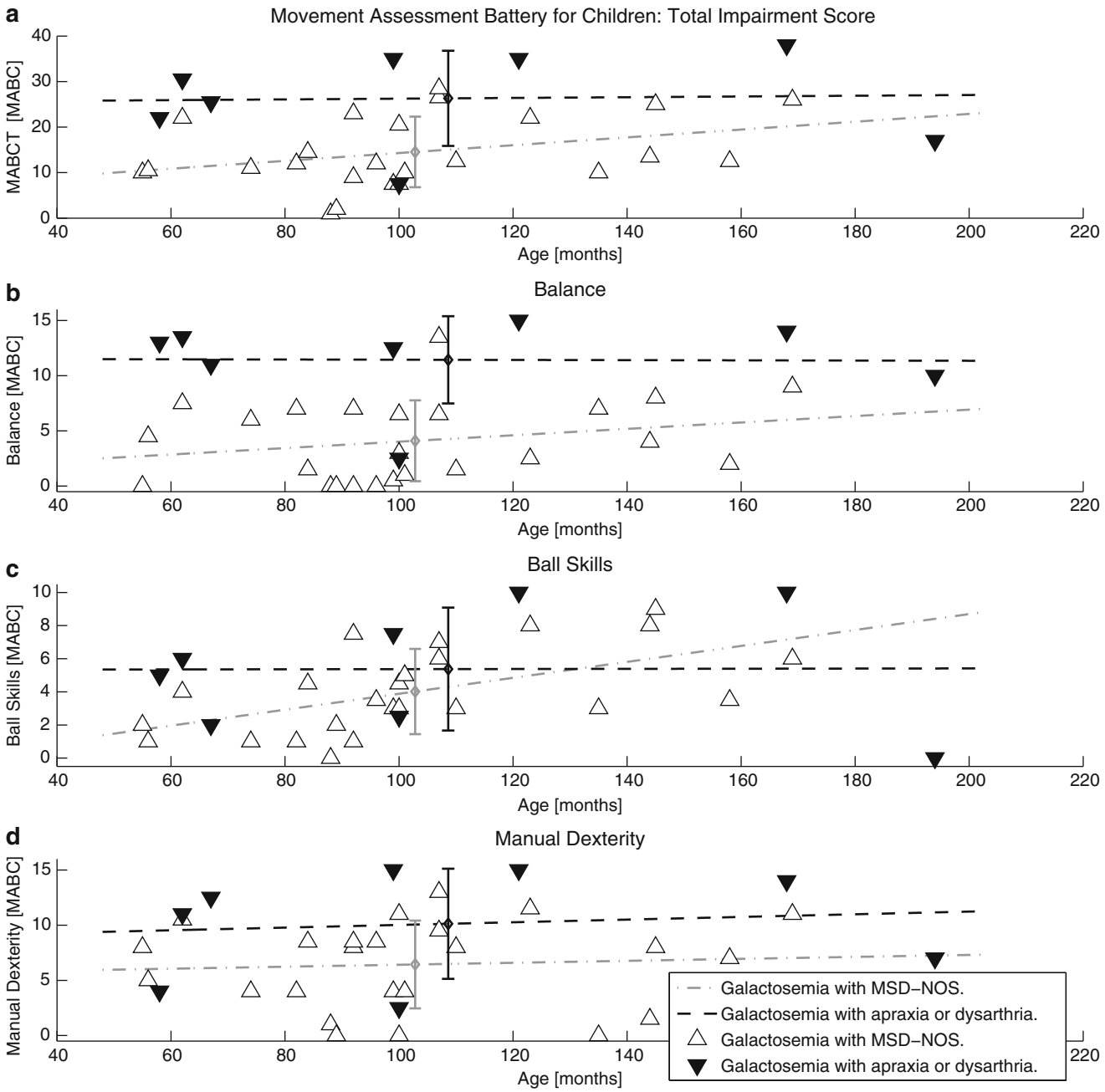

Fig. 3 MABC total and subtests scores for children with galactosemia. Greater MABC total impairment scores correspond to greater impairment. Means and standard deviations shown by diamonds and whiskers

associated with neurologic speech disorders (Murdoch et al. 1995; Robin et al. 1991). This premise was supported by the findings of the present study as all the children with galactosemia had neurologic speech disorders and, on average, had weaker tongues when compared to the controls. Although the mean tongue strength was decreased in children with galactosemia, the rate of increase in tongue strength across ages was equivalent for males and females with galactosemia and the controls. If decreased tongue strength was a causative factor for speech disorders, we would expect that least intelligible children, those with CAS or dysarthria, would have the weakest tongues. Our findings showed that the children with CAS or dysarthria had equivalent tongue strength when compared to the children with MSD-NOS. The relationship of tongue strength to speech competence is controversial in the field of speech-language pathology. Although there is little empirical evidence supporting this practice, most speech-language pathologists (up to 85 %) use nonspeech exercises to attempt to strengthen tongues with the goal of improving

Table 1 Relationships among measures of strength and coordination by gender (left) and by motor speech disorder classification (right)

	n	Dominant hand strength ρ (P)	Nondominant hand strength ρ (P)	Tongue strength ρ (P)	n	Dominant hand strength ρ (P)	Nondominant hand strength ρ (P)	Tongue strength ρ (P)
	Males				**Motor speech disorders-not otherwise specified (MSD-NOS)**			
Balance	21	−.59 (0.007)**	−.60 (0.005)**	−.51 (0.01)*	24	−.37 (0.08)	−.37 (0.09)	−.46 (0.03)*
Ball skills	21	−.49 (0.03)*	−.53 (0.02)*	−.46 (0.04)*	24	−.07 (0.76)	−.16 (0.46)	−.34 (0.11)
Manual dexterity	21	−.66 (0.002)**	−.56 (0.01)*	−.68 (0.0009)***	24	−.38 (0.08)	−.40 (0.06)	−.46 (0.03)*
MABC total score	21	−.67 (0.001)**	−.69 (0.0008)***	−.62 (0.004)**	24	−.37 (0.08)	−.46 (0.03)*	−.56 (0.006)**
	Females				**Childhood apraxia of speech (CAS) or dysarthria**			
Balance	11	−.46 (0.18)	−.56 (0.10)	−.49 (0.15)	8	−.56 (0.19)	−.43 (0.34)	−.47 (0.29)
Ball skills	11	.19 (0.59)	.25 (0.48)	−.18 (0.62)	8	−.36 (0.43)	−.18 (0.74)	−.22 (0.64)
Manual dexterity	11	−.32 (0.37)	−.32 (0.37)	−.34 (0.34)	8	−.51 (0.24)	−.56 (0.18)	−.67 (0.10)
MABC total score	11	−.39 (0.26)	−.44 (0.21)	−.60 (0.06)	8	−.62 (0.14)	−.42 (0.34)	−.56 (0.18)

Higher scores on the MABC subtests and total score indicate more difficulties. Higher scores on strength indicate greater strength

*Difference at $P < 0.05$ according to Two-Sample Spearman rank correlation

**Difference at $P < 0.01$ according to Two-Sample Spearman rank correlation

***Difference at $P < 0.001$ according to Two-Sample Spearman rank correlation

speech (Lof and Watson 2008). Findings from the present study of children with galactosemia suggest that tongue strength is not related to the type or severity of their motor speech disorder.

Hand strength is a strong indicator of disability and was included in the protocol to look for possible evidence of unilateral versus bilateral involvement and differences across genders (Gallup et al. 2007). In the present study, there was no evidence of unilateral involvement as both participants with galactosemia and control participants showed little variability in strength between their dominant and nondominant hands. Therefore, handedness is discussed next without differentiating between dominant and nondominant laterality. Males and females showed different patterns in hand strength development. Similar to previous studies of normal hand strength development, it increased in parallel in the male and female controls until 10 years of age, after which it increased faster in the males than the females (Häger-Ross and Rösblad 2002). Unlike the controls, males and females with galactosemia had similar hand strength across all ages. At 4–6 years of age, the males with galactosemia had slightly greater hand strength compared to the male controls, but then increased slowly across age, resulting in significantly weaker hand strength throughout adolescence. Hand strength in males is closely related to testosterone levels prenatally and during adulthood (Gallup et al. 2007). Small studies of adolescent males with galactosemia have reported that pubertal development may be delayed in up to 20 % of males although testosterone levels are near normal pre- and post-puberty (Gubbels et al. 2012). This area needs further study as adult males with galactosemia have slightly lower testosterone levels. Females with galactosemia had weaker hand strength across all ages but increased at approximately the same rate as the female controls. Females have varying levels of testosterone and these levels are not related to hand strength in females (Gallup et al. 2007). The decreased tongue and hand strength observed in males and females with galactosemia may have different contributing factors including galactose-1-phosphate levels during the prenatal period, central nervous system white matter deficits (Dubroff et al. 2008; Hughes et al. 2009), or hormone levels during childhood or adolescence (Gallup et al. 2007; Gubbels et al. 2012). Further study examining the relationship between hormone levels and strength is warranted as >80-90 % of females with galactosemia experience gonadal failure (Fridovich-Keil et al. 2011). The prevalence of decreased strength may be inflated due to the inclusionary criteria specifying that children with galactosemia must have a speech disorder to participate in the present study, thereby increasing their risk of other co-occurring disorders.

Coordination

In our study, two-thirds (66 %) of the children with galactosemia had a co-occurring coordination disorder, compared to only one-third (33.7 %) of the general pediatric population who have developmental disorders (Pieters et al. 2012). As a large retrospective survey reported that 60 % of individuals with galactosemia had speech disorders and 18 % had motor disorders, with no mention of co-occurrence (Waggoner et al. 1990), we predicted that approximately one third of the children with galactosemia would have co-occurring speech and coordination disorders. Our data indicates that children with galactosemia have 3.5 times the odds of having a co-occurring coordination disorder compared to the general population with developmental disorders. Of the three domains assessed by the MABC, manual dexterity (speed and accuracy), ball skills (eye-hand coordination), and balance (Henderson and Sugden 1992), balance was severely affected and manual dexterity was moderately affected in children with galactosemia. Children with CAS or dysarthria had poorer balance and manual dexterity than most of the children with MSD-NOS, providing further evidence that a common etiology may underlie motor speech and coordination disorders. As poor balance is characteristic of cerebellar involvement, it was not surprising that the single participant with ataxic dysarthria had significant balance difficulties; however, we did not expect the children with CAS to have equally poor balance, consistent with cerebellar involvement in CAS.

Determining potential predictors of outcomes and a progression of outcome severity in galactosemia has been challenging as each individual is uniquely affected (Waisbren et al. 2012). This lack of a predictable progression of outcomes was evident in the puzzling finding that tongue strength, but not hand strength, was related to poor balance and manual dexterity in participants with galactosemia and MSD-NOS and the lack of association between strength and coordination in participants most severely affected by disordered speech, strength, and coordination. The difference in relationships among coordination and strength across genders provides more evidence that galactosemia differentially affects individuals. For males with galactosemia, poor coordination was related to decreased strength, but the same association was not apparent in females.

Days on Milk

Previous studies (Berry and Elsas 2011; Jumbo-Lucioni et al. 2012) have not found clear associations among long-term complications in galactosemia and the number of days of lactose ingestion during the neonatal period. In the present study, strength and balance were not associated with early dietary lactose ingestion in the children with galactosemia; however, the days of milk ingestion was related to a mild decrease in speech articulation (PCC:AT and PCC:CS) in males only. There was no association between days on milk and percentage of speech errors in females. The association between speech errors and days on milk may be a result of the increased vulnerability of males to neurodevelopmental disorders, a well-documented but poorly understood finding (Pieters et al. 2012). Our findings support the importance of early notification of galactosemia during the neonatal period (Berry 2012), especially for males, as delays in notification and adoption of a lactose-restricted diet may have long-term adverse effects on speech development. Galactosemia is autosomal recessive and occurs equally in males and females. Interestingly in our sample, which had speech disorders as inclusionary criteria, twice as many families with boys volunteered compared to family with girls. This coincides with the 2:1 male–female incidence of speech and coordination disorders observed in the general population (Pieters et al. 2012; Johnson and Breslau 2000) raising the question for future study of a possible higher incidence of these disorders in males vs. females with galactosemia.

Common Underlying Etiology

The high co-occurrence of motor disorders, the decrease in tongue and hand strength in children with galactosemia and speech disorders, and the poorer balance and manual dexterity observed in children with the most speech errors, support the proposal that motor and speech disorders may be due to a common underlying etiology rather than two distinct disorders (Gaines and Missiuna 2007; Pieters et al. 2012). Imaging studies of individuals with CAS (Belton et al. 2003) and individuals with galactosemia (Dubroff et al. 2008; Hughes et al. 2009) both cite cerebellar deficits (in addition to basal ganglia (striatum) and cerebral left-hemisphere pre- and primary motor areas). Diverse areas of the cerebellum are involved in maintaining balance, refining motor movements, motor learning, and speech production (Doya 2000; Penhune and Steele 2012). Balance is mediated primarily near midline of the cerebellum (Stoodley and Schmahmann 2009), speech in the superior lateral area of the right cerebellar hemisphere, and manual dexterity and motor planning in the right and left lateral cerebellar hemispheres, ipsilateral to the affected hand. Since areas of the cerebellum associated with motor planning, motor movements, and refining speech are remote from the cerebellar areas associated with balance control, the association between severity of the speech deficits and balance suggests a common underlying etiology associated with diffuse damage to the cerebellum rather than distinct focal areas of damage. In future imaging

studies, the superior lateral and midline areas of the cerebellum, in addition to basal ganglia (striatum) and cerebral left hemisphere pre- and primary motor areas, should be considered regions of interest.

Limitations and Recommendations

The findings of this study are limited by the criteria used for participant recruitment. The present study was part of a larger study to delineate the speech characteristics associated with CAS in rare disorders, so only children with galactosemia who had received or were currently receiving speech therapy services and only control participants with no history of speech disorders were included. There is a second possible recruitment bias as parents of children with galactosemia and severe speech disorders may have been more likely to volunteer to participate. In addition, the differences between groups on measures of speech and strength may be inflated, as the controls had not received special education services.

Based on our findings, some suggestions for future research and practice can be made: (1) a motor skills assessment should be included in studies examining long-term outcomes in classic galactosemia, (2) males and females should be analyzed separately as they are differentially affected by galactosemia, and (3) healthcare professionals following children with galactosemia should screen for motor as well as speech disorders.

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One Sentence Synopsis

Children with classic galactosemia and speech disorders are at risk for co-occurring strength and coordination disorders.

Details of the Contributions of Individual Authors

Nancy L. Potter conducted the study and drafted the manuscript, Yves Nievergelt performed the data analyses and assisted in drafting the manuscript, Lawrence D. Shriberg was the PI on the grant that funded the present study, assisted in planning the study, analyzed the speech samples, and edited the manuscript.

Name of One Author Who Serves as Guarantor

Nancy L. Potter accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Details of Ethics Approval

The Institutional Review Boards of the University of Wisconsin-Madison and Washington State University approved this study.

Patient Consent Statement

A parent of each participant provided written consent, children age 12 years and older provided written consent, and children 11 years and younger provided written or verbal informed assent.

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