Visuomotor Performance in *KCNJ11*-Related Neonatal Diabetes Is Impaired in Children With DEND-Associated Mutations and May Be Improved by Early Treatment With Sulfonylureas

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OBJECTIVE—To assess performance on an age-standardized neuromotor coordination task among sulfonylurea-treated *KCNJ11*-related neonatal diabetic patients.

RESEARCH DESIGN AND METHODS—Nineteen children carrying *KCNJ11* mutations associated with isolated diabetes (R201H; $n = 8$), diabetes with neurodevelopmental impairment (V59M or V59A [V59M/A]; $n = 8$), or diabetes not consistently associated with neurodevelopmental disability (Y330C, E322K, or R201C; $n = 3$) were studied using the age-standardized Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI).

RESULTS—Although R201H subjects tested in the normal range (median standard score = 107), children with V59M/A mutations had significantly lower than expected VMI standard scores (median = 49). The scores for all three groups were significantly different from each other ($P = 0.0017$). The age of sulfonylurea initiation was inversely correlated with VMI scores in the V59M/A group ($P < 0.05$).

CONCLUSIONS—Neurodevelopmental disability in *KCNJ11*-related diabetes includes visuomotor problems that may be ameliorated by early sulfonylurea treatment. Comprehensive longitudinal assessment on larger samples will be imperative.

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Neonatal diabetes due to activating mutations in the ATP-sensitive potassium channel genes *KCNJ11* and *ABCC8* responds to oral sulfonylureas instead of insulin (1). Approximately 25% of such patients have associated neurodevelopmental disability termed the developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome, likely related to expression of mutated channels in the brain (2–5). The *KCNJ11* V59M mutation is a common cause of intermediate DEND, characterized by speech, motor, and cognitive impairment without epilepsy (6,7). Cognitive and motor skills improved after sulfonylurea therapy in a few intermediate DEND case reports (8–10); however, systematic assessment of particular impairments using validated instruments has not been performed in aggregate numbers. Here, we report on 19 rare *KCNJ11* neonatal diabetes cases assessed at one time with the same well-researched, age-standardized test.

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RESEARCH DESIGN AND METHODS

Participants

All subjects were evaluated during a 2010 family forum in Chicago, as part of our Monogenic Diabetes Registry (http://monogenicdiabetes.uchicago.edu) (11). All parents provided informed written consent as approved by The University of Chicago institutional review board.

Beery-Buktenica Developmental Test of Visual-Motor Integration

The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) presents drawings of geometric forms in order of increasing difficulty to be copied with paper and pencil for subjects >2 years of age. The VMI is often administered to evaluate visual-motor and visual-perceptual deficits. It has a coefficient α of 0.82, and its validity has been established (12–14). The VMI was individually administered by a single clinician trained in the assessment. Raw scores are converted to age-appropriate standard scores.

Statistical analysis

Statistica (version 10.0; http://www.statsoft.com) was used for all analyses. Nonparametric analysis was performed using the Kruskal-Wallis ANOVA test (with value H) for group comparisons, as well as Spearman correlations.

RESULTS—Nineteen subjects 2.2–20.3 years of age participated in the study. Eight subjects had the R201H mutation characterized by isolated diabetes without neurodevelopmental concerns, eight had V59M or V59A (V59M/A) mutations associated with the intermediate DEND syndrome, and three had mutations that have an inconsistently reported neurodevelopmental phenotype (one each with R201C, Y330C, and E322K) (Table 1). All subjects were being successfully treated with oral sulfonylurea monotherapy.

Overall, no group differences were found in age (Kruskal-Wallis ANOVA group comparison H [2, N = 19] = 1.9; P = 0.39), sex distribution (χ^2 [2] = 0.79; P = 0.68), age of diabetes diagnosis (H [2, N = 19] = 2.1; P = 0.35), or age of treatment initiation (H [2, N = 19] = 2.2; P = 0.33) among the three groups.

The three groups differed significantly (H [2, N = 19] = 12.78787; P = 0.0017) from each other in graphomotor constructional abilities necessary for accurate copying of the VMI geometric figures (Table 1 and Supplementary Fig. 1). Namely, in children with R201H, scores fell within the normal range (median = 107, lower quartile = 93, and upper quartile = 118.5), whereas children with V59M/A scored low to very low (median = 49, lower quartile = 49, upper quartile = 74.5), and scores of children with other mutations were intermediate (median = 89, lower quartile = 65, and upper quartile = 91).

Age at treatment initiation was significantly inversely correlated with VMI scores only in the V59M/A group (Spearman correlation = −0.79, $P < 0.05$) (Supplementary Table 1). All three children with V59M/A who had transitioned to sulfonylureas before their first birthday had standard scores >70, whereas the five children whose treatment started later scored <50 (greater than three SDs below the mean).

CONCLUSIONS—To our knowledge, our study represents the largest cohort of rare *KCNJ11* neonatal diabetic patients undergoing an identical neurodevelopmental assessment at one time. Using a well-validated, age-standardized measure, we show that those with intermediate DEND-associated V59M/A mutations have significant impairment of eye-hand coordination, whereas those with the R201H mutation not associated with neurodevelopmental concerns performed in the normal range. Early treatment with sulfonylureas was associated with better VMI scores in the V59M/A group; however, this observation must be confirmed in larger numbers of patients with more comprehensive longitudinal assessments.

Why mutations such as R201H do not cause a similar level of impairment as seen in V59M/A is uncertain, especially since the diabetes caused by these mutations appears to be equivalent. Given that a few of the R201H and other mutation case subjects exhibited low normal scores, it may be that the VMI is not sensitive enough to quantify mild subclinical difficulty.

Other factors could contribute to the neurodevelopmental concerns in these patients, including diabetic ketoacidosis at diagnosis during a very young age critical for brain development, as well as longer-term metabolic control characterized by prolonged hyperglycemia and sometimes frequent episodes of severe hypoglycemia, which has been associated with a spectrum of visual-spatial, memory, attention, and executive dysfunctions (15).

The current study and previous reports of improved cognitive and motor symptoms after the change in treatment suggest the benefit of sulfonylurea blockade of activated glucose-responsive channels that have an unknown function in the brain (8–10). This implies that sulfonylureas cross the blood-brain barrier; however, the degree to which they do may be a critically important factor and warrants further study.

The three V59M/A subjects who started sulfonylurea therapy before 1 year of age had better VMI scores than the five subjects who did not; however, it remains to be determined whether there is a definitive critical age for treatment. This finding raises hope for prevention of at least some of the neurodevelopmental disability in those who start sulfonylureas at an early age. This bolsters consideration of an empirical trial of sulfonylureas in newly diagnosed neonatal diabetic patients before results of genetic testing are available, given that ATP-sensitive potassium channel mutations cause almost 50% of cases. However, the risk/benefit of sulfonylureas should be carefully considered and should in no way supplant mandatory genetic testing.

Notably, VMI scores in the three V59M/A children treated early were still low and developmental challenges are

Table 1—*Clinical characteristics and results of Beery-Buktenica VMI testing in patients with monogenic neonatal diabetes caused by R201H* (n = 8), *V59M or V59A* (n = 8), *or other* (n = 3) *mutations in* KCNJ11

ID	Mutation	Current age (years)	Sex	Age of diabetes diagnosis (months)	Age of sulfonylurea initiation (months)	Standard scores*
R201H mutation causing isolated diabetes (n = 8)						
0165	R201H	2.7	M	2.0	6	137
0130	R201H	2.9	F	3.5	6	109
0261	R201H	4.4	F	2.0	29	85
0021	R201H	7.7	F	6.0	47	119
0142	R201H	9.1	M	2.5	82	94
0004	R201H	9.2	F	2.0	67	118
0074	R201H	18	M	0.5	177	105
0145	R201H	20.3	F	1.0	227	92
	Median	9.3 (mean)	37.5% M	2.0	57	107
	SD	6.6		1.7	81	17.1
Mutations causing intermediate DEND syndrome (n = 8)						
0260	V59M	2.2	F	3.0	4	91
0178	V59M	2.7	M	4.0	9	77
0259	V59M	3.6	F	1.5	2	72
0258	V59M	4.2	M	1.0	15	<50
0216	V59M	5.3	M	4.5	22	<50
0076	V59M	6	M	6.0	33	<50
0100	V59M	17	F	5.5	178	<50
0257	V59A	5.2	F	5.0	42	<50
	Median	5.8 (mean)	50% M	4.3	19	<50
	SD	4.7		1.8	58	9.8
Mutations causing inconsistent developmental phenotype (n = 3)						
0164	Y330C	3.3	M	2.5	13	65
0088	E322 K	7.1	M	5.0	48	91
0000	R201C	10.6	F	1.0	79	89
	Median	7.0 (mean)	66.7% M	2.5	48	89
	SD	3.7		2.0	33	14.5

F, female; M, male. *Standard scores have a mean of 100 and an SD of 15. Scores greater than three SDs below the mean are reported as <50, but were treated as 49 in all statistical analyses.

likely to persist, as is also likely in rare severe DEND cases not assessed in this study. Future research should clarify factors leading to differences in mutation phenotype and outcome. Efforts should include comprehensive specialty assessment and support of optimal progress and continued collection of data on greater numbers of patients tracking long-term neurodevelopmental outcome. In this regard, the VMI may be useful as a quantifiable marker of longitudinal progress.

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R.P.S. contributed to study design; collected, analyzed, and interpreted data; and wrote the manuscript. K.S. provided biostatical analysis and interpretation of data. B.C.K. provided technical support and analyzed and interpreted data. S.A.W.G. designed the study; collected, analyzed, and interpreted data; provided administrative and material support; obtained funding; and supervised the study. M.E.M. designed the study, interpreted data, provided administrative and material support, obtained funding, and supervised the study. All authors reviewed and edited the manuscript, contributed to discussion, and approved the final manuscript. S.A.W.G. and M.E.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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