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

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OBJECTIVE—To assess performance on an age-standardized neuromotor coordination task among sulfonyleurea-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 sulfonyleurea 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 sulfonyleurea 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 sulfonyleureas 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). Cognitively impaired children with sulfonyleurea 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.

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 sulfonyleurea 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 ($\chi^2[2] = 0.79; P = 0.68$), age of diabetes diagnosis ($H[2, N = 19] = 2.1; P = 0.39$), 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 V59mA 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 V59mA group (Spearman correlation $= -0.79, P < 0.05$) (Supplementary Table 1). All three children with V59mA 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 V59mA 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 V59mA 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 V59mA 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 long-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 V59mA 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 V59mA children treated early were still low and developmental challenges are

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**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* |
|----|----------|---------------------|-----|----------------------------------|--------------------------------------|-----------------|
|    |          |                     |     |                                  |                                      |                 |
| 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                                   | 131             |
| 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              |
|     |          |                     |     | SD 6.6                          | 1.7                                   | 81              |
|     |          |                     |     |                                  |                                       | 17.1            |

Mutations causing intermediate DEND syndrome ($n = 8$)

| ID | Mutation | Current age (years) | Sex | Age of diabetes diagnosis (months) | Age of sulfonylurea initiation (months) | Standard scores* |
|----|----------|---------------------|-----|----------------------------------|--------------------------------------|-----------------|
|    |          |                     |     |                                  |                                      |                 |
| 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              |
| 0238 | 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              |
|     |          |                     |     | SD 4.7                          | 1.8                                   | 58              |
|     |          |                     |     |                                  |                                       | 9.8             |

Mutations causing inconsistent developmental phenotype ($n = 3$)

| ID | Mutation | Current age (years) | Sex | Age of diabetes diagnosis (months) | Age of sulfonylurea initiation (months) | Standard scores* |
|----|----------|---------------------|-----|----------------------------------|--------------------------------------|-----------------|
|    |          |                     |     |                                  |                                      |                 |
| 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              |
|     |          |                     |     | 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.
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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 biostatistical 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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