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Patients with *KCNJ11*-related diabetes frequently have neuropsychological impairments compared with sibling controls

D. Carmody[1], A. N. Pastore[1], K. A. Landmeier[2], L. R. Letourneau[1], R. Martin[3], J. L. Hwang[1], R. N. Naylor[1], S. J. Hunter[3], M. E. Msall[2], L. H. Philipson[1], M. N. Scott[3] and S. A. W. Greeley[1]

[1]Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, [2]Kennedy Research Center on Intellectual and Developmental Disabilities, Section of Developmental and Behavioral Pediatrics and [3]Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, Chicago, USA

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Abstract

Aims *KCNJ11*-related diabetes is the most common form of permanent neonatal diabetes and has been associated with a spectrum of neurodevelopmental problems. We compared neurodevelopmental outcomes in patients with *KCNJ11* mutations and their sibling controls.

Methods Through our Monogenic Diabetes Registry (http://monogenicdiabetes.uchicago.edu/), we evaluated 23 patients with *KCNJ11* mutations with (n = 9) and without (n = 14) global developmental delay successfully treated with sulfonylurea and 20 healthy sibling controls, using a battery of targeted neuropsychological and behavioural assessments with scaled scores that are comparable across a wide range of ages.

Results Patients with *KCNJ11*-related diabetes without global developmental delay had significant differences compared with sibling controls on a range of assessments including IQ, measures of academic achievement and executive function. *KCNJ11* patients with global delay exhibited significant differences in behavioural symptoms with a tendency to avoid social contact and displayed a reduced ability to adapt to new circumstances. Parents reported more immature behaviour, gross mood swings, bizarre thoughts, other unusual and severe behaviours, and there were also significant deficits in all subdomains of daily living skills.

Conclusions This series represents the largest and most comprehensive study of neuropsychological and behavioural dysfunction of individuals with *KCNJ11* diabetes and is the first to compare outcome with sibling controls. Our data demonstrate the variety of neurodevelopmental problems seen in those with *KCNJ11* mutations, even in those without recognized global developmental delays. These data can be used to counsel families and guide structured neurodevelopmental assessments and treatments based on the initial genetic diagnosis in patients with neonatal diabetes.

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Introduction

Neonatal diabetes mellitus is a predominantly monogenic disorder and occurs in approximately 1 in 90 000–160 000 live births [1–5]. There are an expanding list of over 25 genes identified associated with neonatal diabetes but many of these are syndromic, with clinical clues that can direct genetic testing [6]. Heterozygous activating mutations in the ATP-sensitive potassium (K_{ATP}) channel genes *KCNJ11* and *ABCC8* are the most common causes of permanent neonatal diabetes and usually allow for treatment with oral sulfonylureas instead of insulin [7,8].

Correspondence to: Siri Atma W. Greeley. E-mail: sgreeley@uchicago.edu

Many patients with K_{ATP}-related neonatal diabetes also exhibit a spectrum of neurodevelopmental problems, from mild learning disorders to significant cognitive dysfunction as well as seizures [9]. These developmental impairments are likely due to mutated K_{ATP} channels that are widely expressed in the brain; however, the possibility that early diabetes and consequent glycaemic excursions might contribute to such dysfunction has not been addressed in a systematic fashion [10,11]. Further evidence for the role of K_{ATP} channel activity in pathogenesis of these neurological problems is that sulfonylurea treatment can produce measureable improvement in neurodevelopmental outcomes in some patients [12]. Those with the constellation of developmental delay, epilepsy and neonatal diabetes have been

What's new?

- The current series represents the largest and most comprehensive study of neuropsychological and behavioural dysfunction in individuals with *KCNJ11*-related diabetes, in whom such impairment is likely due to brain expression of mutated channels.
- The study is the first to provide detailed information on sibling controls, which was essential for demonstrating significant differences on a range of assessments including IQ, measures of academic achievement and executive function, even in subjects without any history of global developmental delay.
- *KCNJ11* patients with global delay exhibited significant differences in behavioural symptoms, as well as significant deficits in all subdomains of daily living skills.

referred to as having developmental delay, epilepsy, neonatal diabetes (DEND) or intermediate DEND (iDEND) syndrome. Although those without obvious neurodevelopmental impairment have been considered to have neonatal diabetes in isolation, it remains unclear whether these patients might also have milder dysfunction [13].

We used a variety of behavioural and neuropsychological assessments to compare children with *KCNJ11*-related neonatal diabetes (with and without DEND/iDEND) with healthy sibling controls. We aimed to identify appropriate early behavioural and developmental measures to aid clinicians and families confronted by this common genetic form of neonatal diabetes. We further hypothesized that those without gross delay would also have differences in at least some measures in comparison with sibling controls.

Methods

Patients with *KCNJ11*-related permanent neonatal diabetes and their unaffected siblings were consented for participation through the University of Chicago Monogenic Diabetes Registry (http://monogenicdiabetes.uchicago.edu/registry/). The Registry collects longitudinal information regarding diagnosis and treatment of diabetes, other medical problems or complications, family history of diabetes, and results of genetic testing through surveys and medical records. All patients were consented for participation through protocols approved by the Institutional Review Board at the University of Chicago.

We carried out standardized neuropsychological and behavioural assessments that allowed for scaled scores comparable across a wide range of ages, thus allowing for a larger number of patients to participate. These measures included Wechsler Abbreviated Scales of Intelligence (WASI-II), Delis–Kaplan Executive Function System (D–KEFS) Trail Making Test, Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span subtest, Wechsler Intelligence Scale for Children (WISC-IV) Digit Span subtest and Wechsler Individual Achievement Test (WIAT-III) (Table S1). Parental report forms of the Behavior Assessment System for Children (BASC-2), the Behavior Rating Inventory of Executive Function (BRIEF) and the Vineland Adaptive Behavior Scales were also used.

Patients were divided into three groups based on clinical phenotypes: *KCNJ11*-related neonatal diabetes with global developmental delay (DEND or iDEND), *KCNJ11*-related neonatal diabetes without global developmental delay, and healthy sibling controls. Patients were considered to have global developmental delay if they were previously reported to have significant delays in two or more developmental domains: gross motor, fine motor, speech and language, cognition, personal and social development, or activities of daily living.

Results are expressed as mean ± SD unless indicated. Data from pre-school Behavior Rating Inventory of Executive Function assessment (BRIEF-P) for children aged 2–5 years was combined with data from the BRIEF assessments completed by parents for those aged 5–18 years. Data were analysed using GraphPad Prism 6 (GraphPad Software, CA, USA, http://www.graphpad.com). Nonparametric analyses were performed using the Kruskal–Wallis analysis of variance (ANOVA) test or Mann–Whitney *U*-test for group comparisons. Group differences were considered significant if $P < 0.05$.

Results

Twenty-three subjects with *KCNJ11*-related neonatal diabetes, including nine with global developmental delay (seven V59M, one V59A and one Y330C) and 14 without global delay (seven R201H, three R201C, one W68C, one E322K, one R50Q and one A174G), and 20 sibling controls participated in the study (Table 1). The majority of individuals with *KCNJ11*-related neonatal diabetes with global developmental delay were unable to complete the assessments of intellectual and executive functioning due to the severity of their delay.

Assessments of intellectual and executive function

We compared 10 patients with *KCNJ11*-related neonatal diabetes without global developmental delay and 10 sibling controls (Table 2). Only two subjects with *KCNJ11*-related neonatal diabetes with global developmental delay were able to complete some assessments of intellectual and executive functioning, with scores consistently lowest of all those assessed (data not shown).

Individuals with *KCNJ11*-related neonatal diabetes without global developmental delay had significant differences in executive functioning, especially when compared with sibling controls (Table 2). Those with mutations in *KCNJ11* had reduced general intellectual ability based on both the matrix

Table 1 Study participants

	KCNJ11-related neonatal diabetes with global developmental delay	*KCNJ11*-related neonatal diabetes without delay	Sibling controls
n	9	14	20
Age at sulfonylurea initiation (years)	1.13 (0.43–8.35)	6.04 (1.24–13.73)	Not applicable
Age at assessment (tears)	7.21 (5.83–12.90)	11.44 (6.52–17.93)	9.23 (6.70–11.16)
Female (%)	5 (55.6)	8 (57.1)	10 (50.0)
Mutations	7 × V59M 1 × V59A 1 × Y330C	7 × R201H 3 × R201C 1 × R50Q, W68C, A174G, E322K	Not applicable

Data are given as medians with interquartile ranges in parentheses.

Table 2 Assessments of intellectual and executive function

	KCNJ11-related neonatal diabetes without delay	Sibling controls	*P*-value
WASI-II (n)	10	9	
IQ	91.1 ± 11.3	111.0 ± 8.3	< 0.005
Matrix reasoning	47.9 ± 7.1	55.1 ± 8.9	NS (0.09)
Matrix vocabulary	48.1 ± 4.5	58.8 ± 6.4	< 0.01
D-KEFS (*n*) (Scaled Score)	9	7	
Condition 1: Visual scanning	8.0 ± 2.2	11.7 ± 2.7	< 0.01
Condition 2: Number sequencing	8.2 ± 3.0	11.57 ± 2.4	< 0.05
Condition 3: Letter sequencing	8.0 ± 2.5	11.0 ± 4.7	< 0.05
Condition 4: Number–letter switching	7.6 ± 2.8	9.86 ± 3.3	NS
Condition 5: Motor speed	9.9 ± 1.6	10.6 ± 3.9	NS
WISC-IV (*n*) (Standard Scores)	9	9	
Backward	7.7 ± 2.4	11.4 ± 2.2	< 0.005
Forward	7.6 ± 1.8	10.7 ± 1.6	< 0.005
Combined	7.1 ± 1.9	11.0 ± 1.7	< 0.001
WIAT-III (*n*) (Standard Scores)	10	10	
Numerical	93.7 ± 11.5	102.5 ± 14.7	NS
Spelling	99.9 ± 14.3	103.3 ± 15.3	NS
Reading	95.9 ± 9.5	110.4 ± 11.0	< 0.01

NS, not statistically significant.

reasoning and vocabulary assessments of the WASI-II. The *KCNJ11* group was also noted to perform worse in the areas of visual scanning speed, number sequencing and letter sequencing assessed through the D-KEFS Trail Making Test. The WISC-IV revealed gross deficits in auditory working memory in those with a *KCNJ11* mutation, with the WISC-IV Digit Span test revealing difficulty with manipulation of verbal information. Word reading difficulties were also evident in those with mutations, as assessed by the WIAT-III.

Behavioural assessments

We used dedicated behavioural assessments to compare six patients with *KCNJ11*-related neonatal diabetes with global developmental delay, nine patients with *KCNJ11*-related neonatal diabetes without global developmental delay, and fourteen sibling controls. Those with *KCNJ11*-related neonatal diabetes, both with and without global developmental delay, had significant differences in behavioural symptoms (Tables 3 and 4). Individuals with mutations in *KCNJ11* demonstrated global deficits across four metacognition scales of executive functioning and also exhibited an inability to control impulsive behaviour, as assessed using the BRIEF.

Those with mutations in *KCNJ11* have a tendency to avoid social contact and display a reduced ability to adapt in new circumstances. Behavioural characteristics reported on the BASC-2 more frequently in those with *KCNJ11* mutations are: immature behaviour, gross mood swings, bizarre thoughts, other unusual and severe behaviours, and being considered 'odd'. Vineland-II results suggested significant deficits in all subdomains of daily living skills (personal, domestic and community) in those with *KCNJ11*-related neonatal diabetes.

Discussion

To our knowledge, this series represents the largest and most comprehensive study of neuropsychological and behavioural dysfunction of individuals with *KCNJ11* diabetes, and is the first to provide detailed information on sibling controls. Our data support previous reports of those with K_{ATP} mutations noting a variety of neurodevelopmental problems that are likely due to direct effects of mutated K_{ATP} channels that are widely expressed in the brain [11].

As expected, those patients with a history of readily apparent global developmental delay (consistent with iDEND/DEND phenotype) had gross neurodevelopmental deficits that precluded their ability to complete many of the instruments utilized in our study. The more novel finding of our study is that the individuals who have mutations not associated with global developmental delay also had a milder degree of neurodevelopmental dysfunction. Intellectual and academic domains were significantly different between those

Table 3 Behavior Assessment System for Children (BASC-2)

	KCNJ11-related neonatal diabetes with global developmental delay	*KCNJ11*-related neonatal diabetes without delay	Sibling controls	ANOVA *P*-value	*KCNJ11*-related neonatal diabetes without delay vs. controls
BASC-2 (*n*) (*T* scores)	6	9	14		
Externalization problems	59.3 ± 8.2	51.4 ± 8.0	46.5 ± 11.1	< 0.05	NS
Internalization problems	46.3 ± 9.0	52.0 ± 9.5	46.3 ± 11.4	NS	NS
Behavioural Symptoms Index	61.2 ± 10.3	50.7 ± 7.6	45.1 ± 9.2	< 0.05	NS
Adaptive skill	33.7 ± 15.4	50.3 ± 10.5	52.4 ± 9.5	NS (0.08)	NS
Mean score of BSI	58.2 ± 7.9	49.0 ± 4.5	46.4 ± 7.0	< 0.05	NS
Mean score of adaptive skills	36.5 ± 13.4	52.1 ± 7.9	52.2 ± 7.9	NS (0.07)	NS
Hyperactivity	65.3 ± 12.7	51.2 ± 8.5	50.4 ± 15.2	< 0.05	NS
Aggression	52.0 ± 6.4	51.6 ± 7.7	45.6 ± 9.9	NS (0.06)	NS (0.09)
Conduct problems	54.3 ± 8.2	50.0 ± 17.5	43.5 ± 10.0	NS	NS
Anxiety	42.5 ± 11.1	55.9 ± 12.3	50.1 ± 8.8	NS	NS
Depression	53.8 ± 13.8	51.6 ± 7.7	47.3 ± 9.4	NS	NS
Somatization	52.3 ± 7.0	47.1 ± 6.5	43.6 ± 11.6	< 0.05	NS
Atypicality	63.8 ± 13.3	49.6 ± 8.4	43.7 ± 4.6	< 0.005	NS (0.09)
Withdrawal	56.0 ± 8.2	48.1 ± 9.2	42.9 ± 4.5	< 0.05	NS
Attention problems	64.8 + 14.0	50.1 + 11.1	48.1 + 11.2	NS (0.05)	NS
Adaptability	37.7 ± 5.4	48.9 ± 10.5	52.3 ± 8.9	< 0.05	NS
Social skills	43.8 ± 15.4	51.8 ± 9.1	54.6 ± 9.8	NS	NS
Leadership skills	36.7 ± 13.8	52.3 ± 13.1	56.5 ± 7.8	NS (0.08)	NS
Activities of daily living	30.2 ± 14.7	48.4 ± 9.5	50.7 ± 10.4	< 0.05	NS
Functional communication	33.5 ± 14.8	51.4 ± 12.5	49.6 ± 8.1	NS	NS

NS, not statistically significant.

with *KCNJ11*-related neonatal diabetes without global developmental delay and sibling controls: specifically IQ, vocabulary development (both on WASI-II) and reading achievement (WIAT-III). Individuals with *KCNJ11*-related neonatal diabetes without delay had lower performance than sibling controls in all measures of academic achievement, although a statistically significant difference was found only for reading scores. Compared with sibling controls, patients with *KCNJ11*-related neonatal diabetes without global delay showed difficulties in many areas of executive functioning on several different measures that we utilized: planning, organizing, strategizing, paying attention to and remembering details, and managing time and space. Thus patients with *KCNJ11*-related neonatal diabetes who are not phenotypically categorized as having developmental delays may still have significant deficits in several critical neurodevelopmental areas. Although these patients appear in most cases able to have reasonably normal overall function, a better understanding of their underlying struggles would allow for more effective individual supports and/or accommodations. For example, the sibling controls had a higher-than-average level of achievement for IQ on the WASI-II (111.0 ± 8.3), whereas the *KCNJ11* patients without global delay were lower than average (91.1 ± 1.3). Larger sample sizes may better define such group differences and identify subtle differences within mutation subtypes.

When analysing behaviour, communication, socialization and motor skills, several significant differences were noted between patients with *KCNJ11*-related neonatal diabetes with and without global delay and sibling controls. Patients with *KCNJ11*-related neonatal diabetes showed more problematic behavioural traits including: externalizing behaviour problems, hyperactivity, somatization, atypicality, withdrawal, adaptability and difficulty with activities of daily living. Executive functioning weaknesses seen in individuals with mutations in *KCN11* likely contribute to the behavioural and academic problems reported by their parents on other standardized rating scales. Although specific impairments in hand–eye tracking have been noted, our study and others would suggest more global deficits are associated with K_{ATP} mutations [9,14].

Although prior evidence strongly suggests that specific K_{ATP} channel mutations impart different degrees of neurodevelopmental impairment, because previous reports have been inconsistent in the degree of impairment exhibited by individuals with specific mutations, we chose to categorize patients according to overall developmental phenotype: those with or without global developmental delay. The fact that all patients with certain *KCNJ11* mutations previously associated with significant impairment (e.g. V59M) were in the global delay category further supports the notion that impairment is mutation-dependent; however, our study also shows substantial interindividual variation among those with the same mutation and thus emphasizes the need to study larger numbers of patients over time to delineate the factors influencing neurodevelopmental outcome, such as the age of initiation of sulfonylurea therapy.

Careful characterization of the mutation-specific neurodevelopmental problems may allow us to determine the potential beneficial cognitive effects of sulfonylurea

Table 4 Behavior Rating Inventory of Executive Function (BRIEF) and Vineland Adaptive Behavior Scales

	KCNJ11-related neonatal diabetes with global developmental delay	*KCNJ11*-related neonatal diabetes without delay	Sibling controls	ANOVA *P*-value	*KCNJ11*-related neonatal diabetes without delay vs. controls *P*-value
BRIEF (*n*) (*T* scores)	5	10	14		
Inhibit	71.6 ± 10.6	59.2 ± 13.7	50.0 ± 11.9	< 0.05	NS (0.09)
Shift	61.4 ± 9.4	54.3 ± 10.4	46.9 ± 8.8	< 0.05	NS
Emotional control	61.8 ± 13.2	50.4 ± 12.2	49.6 ± 10.3	NS	NS
Working memory	72.3 ± 7.1	61.3 ± 13.1	48.2 ± 11.7	< 0.01	< 0.05
Plan/organize	64.4 ± 10.7	59.7 ± 14.7	48.1 ± 12.7	< 0.05	< 0.05
Megacognition Index	71.5 ± 6.8	59.9 ± 11.4	47.5 ± 12.8	< 0.01	< 0.05
Global executive composite	72.8 ± 6.8	59.3 ± 12.3	47.6 ± 12.1	< 0.005	< 0.05
Vineland (*n*) (V-scale/ Standard Scores)	7	11	7		
Receptive	12.0 ± 6.2	14.5 ± 4.7	16.0 ± 2.1	NS	NS
Expressive	9.4 ± 4.2	12.5 ± 3.9	17.3 ± 3.3	< 0.01	< 0.05
Written	11.3 ± 8.2	12.1 ± 3.1	15.7 ± 3.7	< 0.05	NS (0.07)
Communication	75.3 ± 33.9	89.8 ± 20.2	109.4 ± 19.2	< 0.05	< 0.05
Personal	9.1 ± 4.4	16.0 ± 4.6	16.4 ± 3.5	< 0.05	NS
Domestic	11.0 ± 3.2	12.7 ± 3.5	15.9 ± 1.9	< 0.05	< 0.05
Community	8.3 ± 4.2	13.7 ± 3.2	17.9 ± 1.6	< 0.001	< 0.05
Daily living skills	69.7 ± 16.8	94.7 ± 15.7	110.0 ± 14.1	< 0.005	NS
Interpersonal	10.3 ± 2.4	12.0 ± 4.0	16.9 ± 1.9	< 0.01	< 0.05
Play and leisure	8.6 ± 2.9	13.0 ± 3.7	15.1 ± 2.4	< 0.01	NS
Coping	10.7 ± 3.2	16.7 ± 3.0	16.7 ± 1.8	< 0.05	NS
Socialization	66.0 ± 7.8	95.2 ± 16.0	107.7 ± 10.9	< 0.005	NS
Adaptive behaviour composite	69.7 ± 19.8	94.8 ± 18.0	107.7 ± 16.5	< 0.05	NS

NS, not statistically significant.

treatment over time. K_{ATP} channels are widely expressed in the brain [10] and just as sulfonylurea therapy usually leads to dramatic improvements in glycaemic control, several reports have documented improvements in various aspects of neurological function following sulfonylurea treatment, although not in all cases [7,9,13,15–21]. Although many factors such as severity of illness at diabetes diagnosis, frequency of hypoglycaemic episodes and long-term degree of glycaemic control may influence the severity of neurodevelopmental impairment as well as the response to sulfonylureas, one important limiting factor may be the degree to which sulfonylurea drugs are able to penetrate the blood–brain barrier and remain in the cerebrospinal fluid [22]. In this regard, one recent imaging study suggests that sulfonylurea can do so at least to some degree in that cerebral perfusion is improved with the administration of sulfonylurea in patients with K_{ATP} channel mutations [23]. Another key consideration is that earlier initiation of sulfonylurea treatment during a potential window of plasticity during early brain development may be critical for optimal neurodevelopmental benefit, as suggested by our previous data showing better outcome on one specific measure in those treated at a very young age [24].

We have shown recently that the age at which the sulfonylurea treatment is started also has a considerable effect on the success of the treatment on glycaemic control, with older patients needing a higher dose of medication to achieve a comparable level of glycaemic control [25]. This suggests some greater difficulty in overcoming long-term changes that may have occurred in β-cell function during the many years in which channel closure was not possible and insulin secretion did not occur. In the same way, it would be expected that significant changes in neurodevelopmental pathways occur over time as a result of the lack of channel closure in the brain and it is likely that not all of these chronic changes will be reversible. It has been suggested that early initiation with higher doses of sulfonylureas may be needed to ensure a high enough concentration to allow effective closure of K_{ATP} channels widely present within the brain [26]. Mutated K_{ATP} channels causing diabetes might also lower the excitability of key neurons, thereby inhibiting their function or that of entire pathways in the brain. Although further study is required to determine the best pharmacological intervention, our data can be used to counsel families and guide structured neurodevelopmental assessments and treatments based on the initial genetic diagnosis in patients with neonatal diabetes. Further study of these defects and how they respond to sulfonylureas may reveal details of neuronal control of the behaviours and functions we studied.

Conclusions

The results of this large series suggest that a multidisciplinary approach to neurodevelopmental testing and support should be provided for all children with *KCNJ11*-related diabetes,

even those without obvious difficulties. In order to ensure such appropriate surveillance and treatment measures are taken, families should be made aware of the potential for neurodevelopmental and behavioural sequelae. Future longitudinal studies aimed at assessing the neurodevelopmental trajectories for each patient will give us further insight into this interesting genetic form of diabetes. In addition, larger collaborative studies may identify mutation-specific and treatment-related outcomes. We encourage clinicians to refer children for standardized assessments of behaviour and development, including evaluation of motor, cognitive, communicative, adaptive and executive functioning, starting from an early age.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cognitive and behavioural assessment instruments.