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Patients with *KCNJ11*-related Diabetes Frequently Have Neuropsychological Impairments Compared to Sibling Controls

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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 subjects with *KCNJ11* mutations and their sibling controls.

Methods—Through our Monogenic Diabetes Registry (<http://monogenicdiabetes.uchicago.edu/>), we evaluated 23 subjects 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—Subjects with *KCNJ11*-related diabetes without global developmental delay had significant differences compared to sibling controls on a range of assessments including IQ, measures of academic achievement and executive function. *KCNJ11* subjects 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 demonstrates the variety of neurodevelopmental problems seen in those with *KCNJ11* mutations, even in those without

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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.

Keywords

Neonatal Diabetes Mellitus; *KCNJ11*; Developmental delay; epilepsy and neonatal diabetes

Introduction

Neonatal diabetes mellitus (NDM) 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 NDM 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 NDM and usually allow for treatment with oral sulfonylureas (SU) instead of insulin [7–8].

Many patients with K_{ATP} -related NDM 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 could 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 referred to as having developmental delay, epilepsy, neonatal diabetes (DEND) or intermediate DEND (iDEND) syndrome. While 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 NDM (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 to sibling controls.

Methods

Subjects with *KCNJ11*-related permanent NDM 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 subjects 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 subjects 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) (Supplemental Table 1). 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.

Subjects were divided into three groups based on clinical phenotypes: *KCNJ11*-related NDM with global developmental delay (DEND or iDEND); *KCNJ11*-related NDM without global developmental delay; and healthy sibling controls. Subjects 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 \pm standard deviation 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 was analyzed using Graphpad Prism 6 (GraphPad Software, CA, USA, <http://www.graphpad.com>). Nonparametric analyses were performed using the Kruskal-Wallis 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 NDM, including nine with global developmental delay (7 V59M, 1 V59A and 1 Y330C) and fourteen without global delay (7 R201H, 3 R201C, 1 W68C, 1 E322K, 1 R50Q, and 1 A174G), and twenty sibling controls participated in the study (Table 1). The majority of individuals with *KCNJ11*-related NDM 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 ten subjects with *KCNJ11*-related NDM without global developmental delay and ten sibling controls (Table 2). Only two subjects with *KCNJ11*-related NDM 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 NDM without global developmental delay had significant differences in executive functioning, especially when compared to sibling controls (Table 2). Those with mutations in *KCNJ11* had reduced general intellectual ability based on both the

matrix 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 subjects with *KCNJ11*-related NDM with global developmental delay, nine subjects with *KCNJ11*-related NDM without global developmental delay, and fourteen sibling controls. Those with *KCNJ11*-related NDM, 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 NDM.

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 with *KCNJ11*-related NDM without global developmental delay and sibling controls: specifically IQ, vocabulary development (both on WASI-II), and reading achievement (WIAT-III). Individuals with *KCNJ11*-related NDM 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 to sibling controls, subjects with *KCNJ11*-related NDM 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 NDM 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), while the *KCNJ11* patients without global delay were lower than average (91.1+/-11.3). Larger sample sizes may better define such group differences and identify subtle differences within mutation subtypes.

When analyzing behaviour, communication, socialization, and motor skills, several significant differences were noted between patients with *KCNJ11*-related NDM with and without global delay and sibling controls. Subjects with *KCNJ11*-related NDM 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 *KCNJ11* likely contribute to the behavioural and academic problems reported by their parents on other standardized rating scales. While 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 subjects 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 inter-individual variation among those with the same mutation and thus emphasizes the need to study larger numbers of subjects 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 SU treatment over time. K_{ATP} channels are widely expressed in the brain [10] and just as SU therapy usually leads to dramatic improvements in glycaemic control, several reports have documented improvements in various aspects of neurologic function following SU treatment, though not in all cases [7, 9, 13, 15–21]. Although many factors such as severity of illness at diabetes diagnosis, frequency of hypoglycemic episodes and long-term degree of glycaemic control may influence the severity of neurodevelopmental impairment as well as the response to SU, one important limiting factor may be the degree to which SU drugs are able to penetrate the blood brain barrier and remain in cerebrospinal fluid [22]. In this regard, one recent imaging study suggests that SU can do so at least to some degree in that cerebral perfusion is improved with administration of SU in patients with K_{ATP} channel mutations [23]. Another key consideration is that earlier initiation of SU 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 SU 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 beta cell function during the many years during 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 SU 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. While 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 SUs may reveal details of neuronal control of the behaviors 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BASC	Behavior Assessment System for Children
BRIEF	Behavior Rating Inventory of Executive Function
DEND	Developmental delay, epilepsy and neonatal diabetes
D-KEFS	Delis-Kaplan Executive Function System
iDEND	Intermediate DEND
K_{ATP}	ATP-sensitive potassium
NDM	Neonatal diabetes mellitus
SU	sulfonylureas
WAIS-IV	Wechsler Adult Intelligence Scale
WASI-II	Wechsler Abbreviated Scales of Intelligence
WIAT-III	Wechsler Individual Achievement Test
WISC-IV	Wechsler Intelligence Scale for Children

References

1. Iafusco D, Massa O, Pasquino B, Colombo C, Iughetti L, Bizzarri C, et al. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. *Acta Diabetol.* 49:405–408. [PubMed: 21953423]
2. Wiedemann B, Schober E, Waldhoer T, Koehle J, Flanagan SE, Mackay DJ, et al. Incidence of neonatal diabetes in Austria—calculation based on the Austrian Diabetes Register. *Pediatr Diabetes.* 11:18–23.
3. Stanik J, Gasperikova D, Paskova M, Barak L, Javorkova J, Jancova E, et al. Prevalence of permanent neonatal diabetes in Slovakia and successful replacement of insulin with sulfonylurea therapy in KCNJ11 and ABCC8 mutation carriers. *J Clin Endocrinol Metab.* 2007; 92(4):1276–82. [PubMed: 17213273]
4. Slingerland A, Shields B, Flanagan S, Bruining G, Noordam K, Gach A, et al. Referral rates for diagnostic testing support an incidence of permanent neonatal diabetes in three European countries of at least 1 in 260,000 live births. *Diabetologia.* 2009; 52(8):1683–5. [PubMed: 19499210]
5. Kanakatti Shankar R, Pihoker C, Dolan LM, Standiford D, Badaru A, Dabelea D, et al. Permanent neonatal diabetes mellitus: Prevalence and genetic diagnosis in the SEARCH for Diabetes in Youth Study. *Pediatr Diabetes.* 2013; 14(3):174–80. [PubMed: 23050777]
6. Greeley SAW, Naylor RN, Philipson LH, Bell GI. Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment. *Curr Diab Rep.* 11:519–532.

7. Pearson ER, Flechtner I, Njølstad PR, Macecki MT, Flanagan SE, Larkin B, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*. 355:467–477. [PubMed: 16885550]
8. Babenko AP, Polak M, Cavé H, Busiah K, Czernichow P, Scharfmann R, et al. Activating Mutations in the ABCC8 Gene in Neonatal Diabetes Mellitus. *New England Journal of Medicine*. 355:456–466.
9. Busiah K, Drunat S, Vaivre-Douret L, Bonnefond A, Simon A, Flechtner I, et al. Neuropsychological dysfunction and neurodevelopmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study [corrected]. *The Lancet Diabetes & Endocrinology*. 1:199–207.
10. Ashcroft FM. Adenosine 5'-triphosphate-sensitive potassium channels. *Annu Rev Neurosci*. 1988; 11:97–118. [PubMed: 2452599]
11. Clark RH, McTaggart JS, Webster R, Mannikko R, Iberi M, Sim XL, et al. Muscle dysfunction caused by a KATP channel mutation in neonatal diabetes is neuronal in origin. *Science*. 329:458–461.
12. Gurgel LC, Crispim F, Noffs MH, Belzunces E, Rahal MA, Moisés RS. Sulfonylurea treatment in permanent neonatal diabetes due to G53D mutation in the KCNJ11 gene: improvement in glycemic control and neurological function. *Diabetes Care*. 30:e108. [PubMed: 17965292]
13. Støy J, Greeley SAW, Paz VP, Ye H, Pastore AN, Skowron KB, et al. Diagnosis and treatment of neonatal diabetes: a United States experience. *Pediatr Diabetes*. 9:450–459. [PubMed: 18662362]
14. McTaggart JS, Jenkinson N, Brittain J-S, Greeley SA, Hattersley AT, Ashcroft FM. Gain-of-function mutations in the K(ATP) channel (KCNJ11) impair coordinated hand-eye tracking. *PLoS ONE*. 8:e62646.
15. Slingerland AS, Hurkx W, Noordam K, Flanagan SE, Jukema JW, Meiners LC, et al. Sulphonylurea therapy improves cognition in a patient with the V59M KCNJ11 mutation. *Diabet Med*. 25:277–281.
16. Koster JC, Cadario F, Peruzzi C, Colombo C, Nichols CG, Barbetti F. The G53D mutation in Kir6.2 (KCNJ11) is associated with neonatal diabetes and motor dysfunction in adulthood that is improved with sulfonylurea therapy. *J Clin Endocrinol Metab*. 93:1054–1061.
17. Slingerland AS, Nuboer R, Hadders-Algra M, Hattersley AT, Bruining GJ. Improved motor development and good long-term glycaemic control with sulfonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the KCNJ11 gene. *Diabetologia*. 49:2559–2563.
18. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. *Pediatr Diabetes*. 11:203–207.
19. Ting W-H, Huang C-Y, Lo F-S, Lee HC, Lin CL, Guo WL, et al. Improved diabetic control during oral sulfonylurea treatment in two children with permanent neonatal diabetes mellitus. *J Pediatr Endocrinol Metab*. 22:661–667.
20. Kim MS, Kim SY, Kim GH, Yoo HW, Lee DW, Lee DY. Sulfonylurea therapy in two Korean patients with insulin-treated neonatal diabetes due to heterozygous mutations of the KCNJ11 gene encoding Kir6.2. *J Korean Med Sci*. 22:616–620.
21. Sagen JV, Raeder H, Hathout E, Shehadeh N, Gudmundsson K, Baevre H, et al. Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: patient characteristics and initial response to sulfonylurea therapy. *Diabetes*. 53:2713–2718.
22. Takanaga H, Murakami H, Koyabu N, Matsuo H, Naito M, Tsuruo T, et al. Efflux transport of tolbutamide across the blood-brain barrier. *J Pharm Pharmacol*. 50:1027–1033.
23. Fendler W, Pietrzak I, Brereton MF, Lahmann C, Gadzicki M, Bienkiewicz M, et al. Switching to sulphonylureas in children with iDEND syndrome caused by KCNJ11 mutations results in improved cerebellar perfusion. *Diabetes Care*. 36:2311–2316.
24. Shah RP, Spruyt K, Kragie BC, Greeley SA, Msall ME. Visuomotor Performance in KCNJ11-Related Neonatal Diabetes Is Impaired in Children With DEND-Associated Mutations and May Be Improved by Early Treatment With Sulfonylureas. *Diabetes Care*. 35:2086–2088.

25. Thurber BW, Carmody D, Tadie EC, Pastore AN, Dickens JT, Wroblewski KE, et al. Age at the time of sulfonylurea initiation influences treatment outcomes in KCNJ11-related neonatal diabetes. *Diabetologia*. :1–6.
26. Ashcroft FM. New uses for old drugs: neonatal diabetes and sulphonylureas. *Cell Metab*. 11:179–181.

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Novelty Statement

- 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* subjects with global delay exhibited significant differences in behavioural symptoms, as well as significant deficits in all subdomains of daily living skills.

Table 1

Study participants

	<i>KCNJ11</i> -related NDM with global developmental delay	<i>KCNJ11</i> -related NDM without delay	Sibling controls
n	9	14	20
Age at SU initiation	1.13 (0.43–8.35)	6.04 (1.24–13.73)	N/A
Age at Assessment	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 x V59M 1 x V59A 1 x Y330C	7 x R201H 3 x R201C 1 x R50Q, W68C, A174G, E322K	N/A

SU, sulfonylurea

N/A, not applicable

Median and Interquartile ranges in parentheses. N/A- not applicable

Table 2

Assessments of intellectual and executive function

	<i>KCNJ11</i> -related NDM without delay	Sibling controls	P
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

Table 3

Behavior Assessment System for Children (BASC-2)

	KCN/II-related NDM with global developmental delay	KCN/II-related NDM without delay	Sibling controls	ANOVA P value	KCN/II-related NDM 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
ADL	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

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

	KCN/II-related NDM with global developmental delay	KCN/II-related NDM without delay	Sibling controls	ANOVA P value	KCN/II-related NDM 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