Cognitive, Neurological, and Behavioral Features in Adults With *KCNJ11* Neonatal Diabetes

Pamela Bowman,[1,2] Jacob Day,[1,2] Lorna Torrens,[3] Maggie H. Shepherd,[1,2] Bridget A. Knight,[1,2] Tamsin J. Ford,[1] Sarah E. Flanagan,[1] Ali Chakera,[1,2] Andrew T. Hattersley,[1,2] and Adam Zeman[1]

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OBJECTIVE

Central nervous system (CNS) features in children with permanent neonatal diabetes (PNDM) due to *KCNJ11* mutations have a major impact on affected families. Sulfonylurea therapy achieves outstanding metabolic control but only partial improvement in CNS features. The effects of *KCNJ11* mutations on the adult brain and their functional impact are not well understood. We aimed to characterize the CNS features in adults with *KCNJ11* PNDM compared with adults with *INS* PNDM.

RESEARCH DESIGN AND METHODS

Adults with PNDM due to *KCNJ11* mutations (*n* = 8) or *INS* mutations (*n* = 4) underwent a neurological examination and completed standardized neuropsychological tests/questionnaires about development/behavior. Four individuals in each group underwent a brain MRI scan. Test scores were converted to *Z* scores using normative data, and outcomes were compared between groups.

RESULTS

In individuals with *KCNJ11* mutations, neurological examination was abnormal in seven of eight; predominant features were subtle deficits in coordination/motor sequencing. All had delayed developmental milestones and/or required learning support/special schooling. Half had features and/or a clinical diagnosis of autism spectrum disorder. *KCNJ11* mutations were also associated with impaired attention, working memory, and perceptual reasoning and reduced intelligence quotient (IQ) (median IQ *KCNJ11* vs. *INS* mutations 76 vs. 111, respectively; *P* = 0.02). However, no structural brain abnormalities were noted on MRI. The severity of these features was related to the specific mutation, and they were absent in individuals with *INS* mutations.

CONCLUSIONS

***KCNJ11* PNDM is associated with specific CNS features that are not due to long-standing diabetes, persist into adulthood despite sulfonylurea therapy, and represent the major burden from *KCNJ11* mutations.**

KCNJ11 gene mutations are the commonest cause of permanent neonatal diabetes (PNDM), which presents in the first 6 months of life and affects 1 in 100,000 live births (1). *KCNJ11* is expressed in the pancreas and brain as well as other tissues and encodes the Kir6.2 subunit of the K_{ATP} channel. In the pancreas, the K_{ATP} channel links increasing blood glucose to insulin secretion, but activating *KCNJ11* mutations prevent channel closure in response to metabolically generated ATP and result in diabetes (2). Clinically, patients present in an insulin-deficient state, and prior to discovery of disease-causing variants in the *KCNJ11* gene, they required insulin therapy. It was later

[1]University of Exeter Medical School, Exeter, U.K.
[2]Exeter National Institute for Health Research Clinical Research Facility, Exeter, U.K.
[3]Kent Neuropsychology Service, Kent and Medway NHS and Social Care Partnership Trust, Gillingham, U.K.

Corresponding author: Pamela Bowman, p.bowman@exeter.ac.uk

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shown that *KCNJ11* PNDM could be treated with sulfonylurea tablets, which bind and close the channel, allowing insulin secretion, excellent metabolic control, and reduced glycemic variability (3). For many patients and their families, transferring from insulin to oral sulfonylureas vastly improved quality of life in relation to diabetes (4).

Central nervous system (CNS) features occur in children with *KCNJ11* PNDM in addition to diabetes. These are thought to result from expression of aberrant K_{ATP} channels in the brain. The precise role(s) of K_{ATP} channels in the human CNS has not been fully elucidated, but rodent studies suggest that they play a role in glucose sensing and homeostasis as well as seizure propagation (5,6). *KCNJ11* is expressed in many brain areas, but there are particularly high levels of expression in the cerebellum (7,8). The cerebellum is well-known for its role in motor learning and coordination (9), but it also has functions relating to language, executive function, and mood; furthermore, cerebellar abnormalities have been linked with autism (10,11). Documented CNS features in children with *KCNJ11* mutations range from subtle neuropsychological impairments that specifically affect attention, praxis, and executive function to the severe and overt Developmental Delay, Epilepsy and Neonatal Diabetes [DEND]/intermediate DEND [iDEND] syndrome (12–15). Other associated features may include psychiatric morbidity, specifically, neurodevelopmental disorders and anxiety disorders, visuomotor impairments, and sleep disturbance (16–18). The severity of the CNS phenotype is related to the genotype. For example, the V59M mutation is frequently associated with iDEND syndrome and neurodevelopmental features, whereas the R201H mutation, previously associated with diabetes alone, has been more recently linked with subtle neuropsychological features (12). Historically, the severity of CNS features was thought to be related to the functional severity of the specific mutation in vitro, although functional interpretation also has to take into account the impact of the mutation on the open probability of the K_{ATP} channel, which will depend on whether it affects channel gating or ATP binding (19–22).

Sulfonylurea treatment results in partial improvement in the CNS features (23–26) and resolution of functional cerebellar and temporal lobe abnormalities on single-photon emission computed tomography (SPECT) scanning (24,27). The improvement in CNS features may be limited as a result of poor penetration of the sulfonylurea across the blood-brain barrier or active transport back out of the brain, leading to subtherapeutic concentrations in the cerebrospinal fluid (CSF) (28). This, and anecdotal clinical experience of greater CNS response with higher doses of sulfonylurea, has prompted clinical recommendations of glyburide doses of ~1 mg/kg/day in people with severe neurological features secondary to *KCNJ11* mutations (29). However, the neurobehavioral features continue to have a huge impact on families despite sulfonylurea treatment (16). This contrasts markedly with the outstanding metabolic response that changed lives by alleviating the anxiety associated with poor metabolic control (4). A key question is whether the CNS features continue to represent the major burden from *KCNJ11* mutations in adult life. To date, all studies characterizing CNS features in *KCNJ11* PNDM have been conducted in predominantly pediatric cohorts (12–14,16,23). However, brain development continues beyond childhood and adolescence (30,31). No study has comprehensively assessed the CNS outcomes in adults with *KCNJ11* mutations.

Mutations in the *INS* gene are a less common cause of neonatal diabetes, accounting for ~10% of cases (1). Heterozygous dominant negative *INS* mutations often affect protein synthesis, resulting in production of structurally abnormal preproinsulin and proinsulin within the β-cell, endoplasmic reticulum stress, and cell death. Individuals with these mutations also typically present with insulin deficiency but, unlike those with *KCNJ11* PNDM, require lifelong treatment with replacement doses of insulin (32). The *INS* gene is not expressed in any significant levels in the brain; therefore, it is very unlikely that individuals with *INS* mutations would display a characteristic CNS phenotype as a direct result of their mutations (33). In fact, there have not been any reports of any such neurological issues—in contrast to those with *KCNJ11* PNDM.

Individuals with PNDM may have long-term CNS sequelae secondary to diabetic ketoacidosis at diagnosis, as seen in type 1 diabetes (34,35). However, cerebral edema in *KCNJ11* PNDM gives rise to a pattern of neurological impairment distinct from that seen as a direct result of brain K_{ATP} channel dysfunction (36). More subtle neurocognitive problems also occur in the presence of diabetes per se, particularly if metabolic control is poor and diabetes is diagnosed before age 7 years (37). Further, individuals with type 2 diabetes are at increased risk of developing Alzheimer disease in later life, and this may in part be due to chronic metabolic disturbance and changes in insulin signaling (38). Indeed, there is evidence from both animal and human studies that insulin plays a key role in central processes including memory and learning (38). The nonspecific diabetes-related cognitive features could confound assessment of CNS phenotype in people with *KCNJ11* mutations; however, people with *INS* mutations are well placed to control for them. There has been no previous detailed comparison of the CNS phenotype in people with *INS* and *KCNJ11* mutations.

The aim of this study was to characterize the neurological and neuropsychological features in adults with *KCNJ11* PNDM compared with these features in adults with *INS* PNDM.

RESEARCH DESIGN AND METHODS

Ethics Approval

Ethics approval was obtained from the National Research Ethics Service Committee South West–Exeter.

Sample Size and Patient Recruitment

We identified 34 patients >16 years old with *KCNJ11* mutations and 9 patients >16 years old with *INS* mutations who had received a molecular genetic diagnosis in Exeter and who had been diagnosed with permanent neonatal diabetes before 6 months of age. We approached potential participants either directly at a neonatal diabetes family event in Exeter or via the consultants in charge of their clinical care. We invited 17 individuals with *KCNJ11* mutations to join the study; of these, 10 agreed to participate. However, two individuals were excluded from the analysis owing to possible confounding factors: one individual (mutation L164P) was excluded because he was taking antipsychotic medication to treat a psychotic illness at the time of the study and had

had a particularly severe initial presentation with diabetic ketoacidosis and 3 days in a coma, and a second individual (mutation V59M) was excluded owing to severe neurological impairment following initial presentation with diabetic ketoacidosis (further clinical characteristics of excluded participants are available in Supplementary Table 1). We approached nine individuals with *INS* mutations, and four agreed to take part. All participants were from the U.K. apart from one, who was from Canada.

Tests

All participants were visited at home or assessed in the Exeter Clinical Research Facility by the same consultant neurologist and consultant clinical neuropsychologist who carried out the history taking using a standard pro forma, neurological examination, neuropsychological assessments, mood questionnaire, and neurodevelopmental screen. If possible, an informant or caregiver was also present to facilitate information gathering. The severity of intellectual impairment and behavioral disturbance in one individual (*KCNJ11–8* [V59M]) meant that it was not possible for him to attempt any of the cognitive tests. Another individual (*KCNJ11–6* [V252G]) did not wish to attempt the Controlled Oral Word Association Test (COWAT) and was unable to understand instructions for the Color Trails Test (CTT). In eight participants (four with *KCNJ11* mutations and four with *INS* mutations), T2-weighted brain MRI scans were performed using a 1.5 Tesla MRI scanner. The scans were reviewed and interpreted by a radiologist and a neurologist who were blinded to the mutation status of the individuals concerned.

Medical/Developmental History and Educational and Professional Attainment

Participants and informants were asked for a standard medical history, the ages at which major milestones were attained, whether learning support was required, and level of education/employment.

Neurological Examination

A full neurological examination was performed. This included assessment of cranial nerves, limb tone, power, reflexes, coordination, and sensation and simple tests of motor sequencing and praxis, comprising two tests of bimanual coordination, one unilateral motor sequencing task (the Luria three hand position test), and copying unfamiliar hand positions and manual miming—both tested in each hand.

Psychiatric and Neurodevelopmental Screen

Current psychological distress was assessed using the Hospital Anxiety and Depression Scale (HADS) questionnaire. The Autism Spectrum Quotient (AQ) was administered to screen for autistic traits.

Cognitive Function

A battery of neuropsychological tests was administered to assess a variety of cognitive domains. The Wechsler Abbreviated Scale of Intelligence (WASI) was used as a brief measure of current intelligence quotient (IQ). The Verbal Paired Associates and Visual Reproduction subtests of the Wechsler Memory Scale (WMS-IV) were used to give a verbal and nonverbal (visual) measure of memory. Subtests of the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV), were administered: cancellation to assess processing speed and digit span (forward and backward) to assess working memory. Subtests of the Visual Object and Space Perception battery (VOSP) assessed visuospatial function: incomplete letters and object decision to test object perception and dot counting and cube analysis to test spatial perception. The COWAT was used to assess aspects of executive function including verbal fluency, self-monitoring, and ability to assimilate and adhere to stipulated rules. The CTT-1 and -2 were used as measures of sustained and divided attention and hand-eye motor coordination and speed. Finally, the Addenbrooke's Cognitive Examination-Revised (ACE-R) was used as a broad screening measure of cognition, providing an assessment of the following cognitive domains: attention/orientation, memory, fluency, language, and visuospatial function.

Functional Assessment

The Cambridge Behavioural Inventory revised (CBI-R) was used to complement the information obtained from the history taking. This measure seeks the opinion of the informant, e.g., caregiver or family member, on the frequency of a range of behaviors in the domains of memory and orientation, everyday skills, self-care, abnormal behavior (e.g., tactlessness, impulsiveness), mood, unusual beliefs, altered eating habits, disturbed sleep, stereotypic and motor behaviors, and altered motivation. For each behavior, the informant assigned a score of 0–4 based on the frequency: scores of 3 (occurring daily) or 4 (occurring constantly) denote a significant behavioral deficit.

Statistical Analysis

Data were analyzed using Excel 2010 and Stata 14. Qualitative data were presented descriptively. Where population normative data were available, neuropsychological test scores were converted to *Z* scores. For VOSP subtests, a pass was a score $\geq$5th population percentile. For comparison of characteristics and outcomes between the *KCNJ11* and *INS* groups, data were analyzed using nonparametric methods (Mann-Whitney *U* test for numerical variables and Fisher exact test for categorical variables). Data are presented as median [range] unless otherwise stated.

RESULTS

Participant Characteristics

Baseline clinical characteristics of the participants are outlined in Table 1; these were similar between individuals with *KCNJ11* mutations and individuals with *INS* mutations.

Neurological Features

Abnormalities on neurological examination were identified in seven of eight *KCNJ11* participants and only one *INS* participant (Table 2).

Developmental History and Educational and Professional Attainment

Developmental histories, level of educational support, and employment history reported for each participant are described in Table 2. Developmental delay or learning difficulties were present in all *KCNJ11* participants, and they continued to require high levels of support as adults. In contrast, the *INS* group did not report major learning difficulties, in keeping with their subsequent employment history and independence in adulthood.

Neurodevelopmental and Psychiatric Features

Four of eight with *KCNJ11* mutations, but none of the participants with *INS* mutations, had features of autistic spectrum disorder either via a clinical diagnosis of autism or an AQ score at or above the threshold suggestive of clinically significant

Table 1—Baseline characteristics in individual *KCNJ11* case subjects and *INS* control subjects and summary of group characteristics

Case	Mutation	Inheritance	Sex	Age (years)	Age at diabetes diagnosis (weeks)	Age at genetic diagnosis (years)	Age at transfer to SU (years)	Treatment (total daily dose)	HbA_{1c} DCCT (%)	HbA_{1c} IFCC (mmol/mol)
KCNJ11 1	G53S	Autosomal dominant	M	32	2	23	23	Glyburide 30 mg, metformin 1 g	9.3	78
KCNJ11 2	R201H	Presumed de novo	F	22	4	15	15 (attempted)	Insulin (restarted after trial of glyburide)	8.1	65
KCNJ11 3	R201H	De novo	M	36	10	29	29	Gliclazide 120 mg	8.1	65
KCNJ11 4	R201C	Presumed de novo	F	36	5	27	34	Glyburide 40 mg	7.0	53
KCNJ11 5	R201C	De novo	M	19	6	13	13	Glyburide 27.5 mg	5.4	36
KCNJ11 6	V252G	De novo	M	28	8	21	21	Glyburide 85 mg	10.8	95
KCNJ11 7	V59M	De novo	F	25	15	17	17	Glyburide 7.5 mg	8.1	65
KCNJ11 8	V59M	De novo	M	17	5	10	11	Glyburide 55 mg	5.9	41
INS 1	C43F	Autosomal dominant	F	35	78	31	N/A	Insulin	NK	NK
INS 2	F48C	Presumed de novo	F	50	5	42	N/A	Insulin	NK	NK
INS 3	G75C	De novo	M	28	8	26	N/A	Insulin	7.9	63
INS 4	H29D	De novo	F	20	26	12	N/A	Insulin (pump)	8.2	66
KCNJ11 group	N/A	De novo = 7 (87.5%), autosomal dominant = 1 (12.5%)	5 (63%) M, 3 (37%) F	26.5 (17–36)	5.5 (2–15)	19 (10–29)	21 (11–34)	1 of 8 insulin treated (12.5%)	8.1 (5.4–10.8)	65 (36–95)
INS group	N/A	De novo = 3 (75%), autosomal dominant = 1 (25%)	1 (25%) M, 3 (75%) F	31.5 (20–50)	17 (5–78)	28.5 (12–42)	N/A	4 of 4 insulin treated (100%)	8.1 (7.9–8.2)	65 (63–66)
P value	N/A	1.0	0.55	0.44	0.15	0.23	N/A	0.01	0.79	0.79

Group summary data are presented as median (range) for continuous numerical data and *n* (%) for categorical data. Individual values are also presented for each participant (continuous and discrete numerical data and categorical data). Mutations were presumed to have arisen de novo if there was no parental history of diabetes but the mutation status of the parents had not been confirmed with a genetic test. HbA_{1c} values are the results available closest to the time of the neurobehavioral assessment. DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry; N/A, not applicable; NK, not known; SU, sulfonylureas.

autistic traits (Table 2 and Supplementary Table 3). Two individuals in the *KCNJ11* group and one in the *INS* group required treatment either at the time of the study or in the past for depression or anxiety. HADS scores for anxiety and depression were similar in *KCNJ11* versus *INS* participants (Supplementary Table 3). One individual in the *KCNJ11* group and two individuals in the *INS* group scored above the HADS clinical threshold (11) for anxiety (Table 2 and Supplementary Table 3).

Cognitive Function

IQ was lower in the *KCNJ11* group versus the *INS* group (IQ 76 [55–101], $n = 7$, and 111 [90–124], $n = 4$, $P = 0.02$). Three individuals in the *KCNJ11* group had an IQ <70 (Supplementary Table 2) and impairments in adaptive behaviors in keeping with a clinical diagnosis of intellectual disability (39). Five of seven individuals in the *KCNJ11* group scored below the clinical cut point for cognitive impairment on the ACE-R (Supplementary Fig. 1). CTT-1 scores suggested reduced attention (CTT-1 Z score -1.7 [-3.0 to -0.1], $n = 6$, vs. 0.4 [-1.1 to 1.2], $n = 4$, $P = 0.03$, and CTT-2 Z score -0.8 [-3.0 to 0.8], $n = 6$, vs. 0.7 [-1.0 to 1.2], $n = 4$, $P = 0.13$) (Fig. 2 and Supplementary Table 2).

In the *KCNJ11* group but not the *INS* group, median scores on the WASI, WAIS, and WMS were below population average in all subtests apart from the verbal paired associates subtest of the WMS (Fig. 1). Scores were particularly low ($\leq$2 SD below population average) in the matrix reasoning component of the WASI (Z score -3.2 [-4.8 to -0.9] vs. 0.6 [-0.7 to 0.8], $P = 0.008$) and the digit span component of the WAIS-IV (Z score -2.0 [-3.0 to 0.3] vs. 0 [-1.0 to 0.3], $P = 0.046$). Cancellation scores, although not as markedly reduced compared with population norms, were significantly lower in the *KCNJ11* group (Z score -1 [-3 to 0] vs. 2.8 [0.7–3.0], $P = 0.007$). COWAT and VOSP scores showed a trend toward reduced executive function and visuospatial function, respectively, in the *KCNJ11* group (Supplementary Table 3), although these did not reach statistical significance.

Behavioral/Functional Impact

In the *KCNJ11* group, 6 individuals had severe behavioral features, which clustered

Table 2—History and examination findings for individual *KCNJ11* case and *INS* control subjects

	History							Examination/investigations	
Case subject (mutation)	Developmental milestones/ interventions	Seizures (cause, if known)	Educational attainment	Learning difficulties/support	Employment status (job)	Employment status (job) of parents/siblings	Psychiatric history	Neurological examination	Brain MRI
KCNJ11 1 (G53S)	D (speech and motor)	No	MS then SS (age 11)	LS (repeated year 2)	E (supermarket)	F – E (council), S – E (chemicals factory)	Repetitive handwashing and rigid routines	Impaired motor sequencing, fine finger movements, praxis. Subtle nystagmus, dysdiadokokinesis	ND
KCNJ11 2 (R201H)	D (speech)	No	MS then U (nursing and childcare)	LS (English until age 15 years, math for 1 year)	US	F – E (accountant), M – E (nurse)	Nil	Intermittent mild head titubation. Brisk reflexes, questionable increase in tone in left arm	N
KCNJ11 3 (R201H)	N	Yes: hypoglycemia on insulin	MS then C (18 months, NVQs levels 1 and 2)	LS (English and math)	E (baker)	NK	Nil	Normal	Bilateral high T1 signal in pons, artifact
KCNJ11 4 (R201C)	N	Yes	MS then C (computing module)	LS (throughout school)	E (pubs, shops, hotel)	B – E (operations manager), S – E (sports complex manager)	Depression: sertraline 50 mg. Occasional auditory hallucinations	Nystagmus (2–3 beats on horizontal gaze), subtle intention tremor	N
KCNJ11 5 (R201C)	D (gross motor, speech). Speech therapy	Yes: hypoglycemia on insulin	MS then C (for people with ID)	LS (from age 10 years)	CS (college for people with ID)	F – E (company manager), M – UE (housewife), B – E (aviation engineer), B – US (political science)	Anxiety (social skills training by psychologist)	Impaired motor sequencing	ND
KCNJ11 6 (V252G)	D (speech, fine motor). Speech therapy	No	SS then school for autistic children	Unable to read/write. Supported accommodation	UE	B – E (carpenter)	Autism	Impaired motor sequencing, praxis, heel-toe walking. Hand flapping	ND
KCNJ11 7 (V59M)	Speech therapy	Yes: hypoglycemia on insulin	MS then C (1st year - childcare)	LS (throughout school)	E (SS teaching assistant)	M – E (SS teaching assistant), F – E (lecturer), B – E (trainee lawyer)	Anxiety	Impaired motor sequencing, dysdiadokokinesis, choreiform movements	N (movement artifact)
KCNJ11 8 (V59M)	D (global)	Yes: hypoglycemia on insulin	SS	Unable to read/write	UE	S – E (museum curator)	Autism	Ritualistic, clumsy, echolalia. Generally uncooperative with examination	ND

Continued on p. 220

Table 2—Continued

Case subject (mutation)	History							Examination/investigations	
	Developmental milestones/ interventions	Seizures (cause, if known)	Educational attainment	Learning difficulties/support	Employment status (job)	Employment status (job) of parents/siblings	Psychiatric history	Neurological examination	Brain MRI
INS 1 (C43F)	N	Yes	U (pharmacy degree)	No	E (hospital pharmacist)	NK	Nil	N	ND
INS 2 (F48C)	N	Yes: hypoglycemia	U (law degree)	No support	UE (ill health). Clerical/caregiver jobs in past	F – E (taxi business manager, security guard)	Depression (medication and CBT in the past), OCD	Depressed leg reflexes (in keeping with known diabetic neuropathy)	Left temporal lobe abnormality, CSF space or artifact
INS 3 (G75C)	N	No	MS	No support	E (department of work and pensions)	F – E (carpenter, transport manager), B – E (marketing agency)	Nil	N	N
INS 4 (H29D)	N	Yes: DKA	MS	LS (math and English, 4 years)	E (bank call center)	F – E (carpenter)	Anxiety, panic attacks (escitalopram in the past)	N	Prominent left cerebellar sulcus, periventricular white matter lesions

B, brother; C, college; CBT, cognitive behavioral therapy; CS, college student; D, delayed; DKA, diabetic ketoacidosis; E, employed; F, father; ID, intellectual disability; LS, learning support; M, mother; MS, mainstream school; N, normal; ND, not done; NK, not known; OCD, obsessive compulsive disorder; S, sister; SS, special school; U, university; UE, unemployed; US, university student.

in the domains of everyday skills (5 of 6), stereotypic behavior (5 of 6), memory and orientation (4 of 6), abnormal behavior (3 of 6), mood (3 of 6), and motivation (3 of 6). Specific everyday skills highlighted included writing (3 of 5) and dealing with money/bills (2 of 5). The most frequent stereotypic behaviors were being rigid/fixed (3 of 5) and having fixed routines (4 of 5). Poor concentration was highlighted as a specific feature in all four individuals who had memory and orientation problems. Two individuals had significant difficulties with self-care, and two reported disturbed sleep.

Neuroimaging

Structural brain MRI was normal in participants with *KCNJ11* mutations. Of *INS* control subjects, two had normal results and two had minor abnormalities that were not clinically significant (Table 2).

Severity of Impairments Associated with the Specific Mutation

Performance on the cognitive tests was better in the two individuals with the R201H mutation. These individuals consistently had scores equal to or greater than the *KCNJ11* group medians (Figs. 1 and 2 and Supplementary Table 2), and no significant behavioral features were reported.

CONCLUSIONS

We have characterized for the first time the profile of neurological, neuropsychological, and behavioral features present in adults with PNDM due to *KCNJ11* mutations. The key features were learning difficulties, features of autism spectrum disorder, subtle motor deficits affecting coordination and motor sequencing, and reduced IQ. Specific cognitive domains most affected were perceptual/nonverbal reasoning, working memory, and attention, with a trend toward executive dysfunction and impaired visuospatial abilities. Verbal paired associate memory was relatively preserved. The impact on everyday functioning was significant; two participants were severely impaired, requiring support with activities of daily living. A comparison group of patients with neonatal diabetes of similar duration due to *INS* mutations did not show any of these specific features, indicating that they are unlikely to be a nonspecific effect of metabolic disturbance from birth. Furthermore, as both

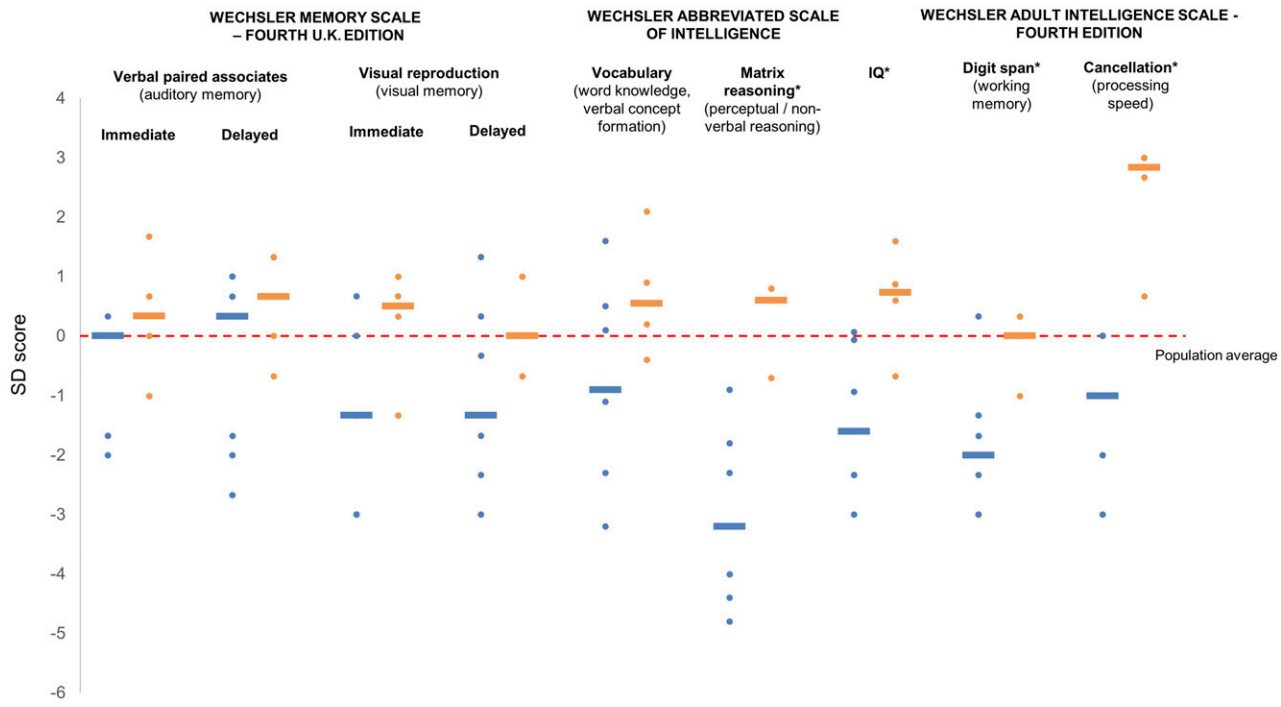

Figure 1—Neuropsychological testing in *KCNJ11* patients (blue) ($n = 7$) and *INS* patients (orange) ($n = 4$). WMS: verbal paired associates I/II (immediate/delayed), auditory memory; visual reproduction I/II (immediate/delayed), visual memory (both components of working memory). WASI: vocabulary, word knowledge, and verbal concept formation; matrix reasoning, nonverbal/perceptual reasoning. WAIS: Digit span, working memory; cancellation, processing speed. *$P < 0.05$ for difference between *KCNJ11* and *INS* groups.

groups were insulin treated from diagnosis as infants, the differences observed are unlikely to have been influenced by variation in the timing or duration of action of insulin on insulin and insulin-like growth factor receptors in the brain.

Our findings are consistent with studies in pediatric cohorts with *KCNJ11* neonatal diabetes. Specifically, the motor features noted on neurological examination, together with impairments of attention, working memory, visuospatial

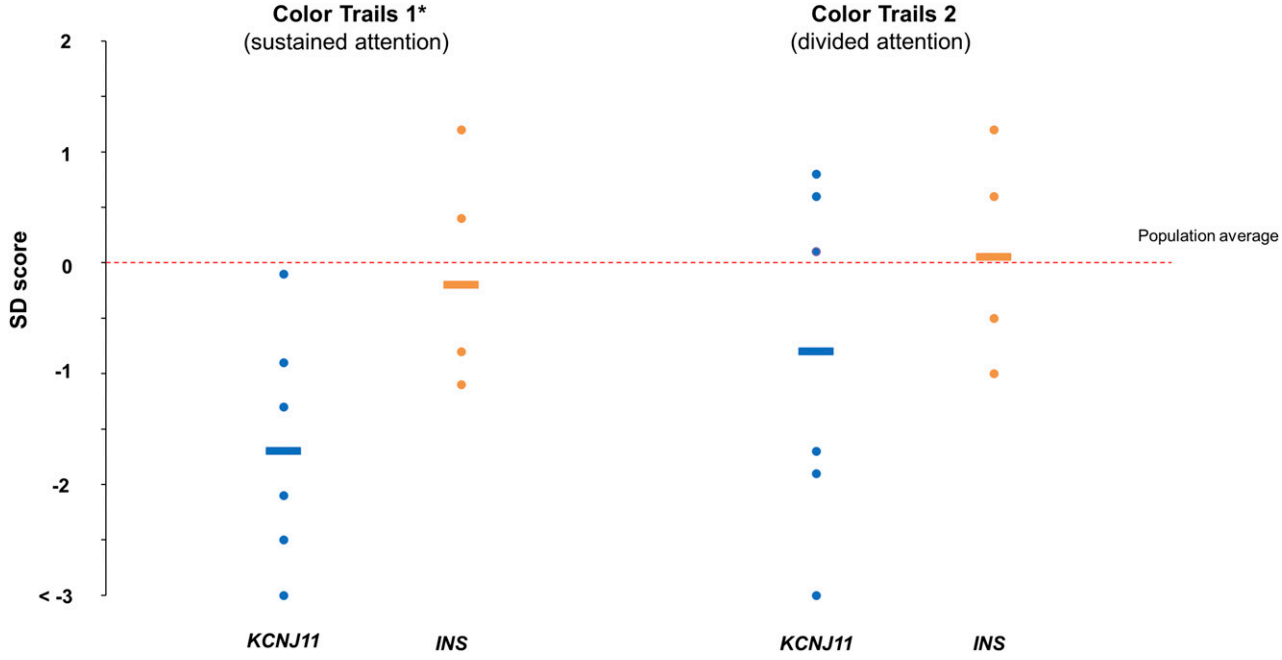

Figure 2—CTT-1 and CTT-2 scores represented as *Z* scores in the *KCNJ11* group (blue) ($n = 6$) and *INS* group (orange) ($n = 4$). Lines show group medians for each subtest; dots represent individuals. *$P < 0.05$ for difference between *KCNJ11* and *INS* groups.

ability, and executive function, are consistent with the previously reported high prevalence of developmental coordination disorder, inattention, executive dysfunction, and poor visuomotor performance in children with *KCNJ11* mutations (12–14,17,18,23,40). Autism spectrum disorder features in four individuals with *KCNJ11* mutations are consistent with previous research reporting high rates of neurodevelopmental disorders in affected children (16,18,41). Dyspraxia, visuomotor impairment, autism, and impaired executive function may be related to the high levels of expression of dysfunctional K_{ATP} channels in the cerebellum in *KCNJ11* PNDM (7,10).

Importantly, the abnormal findings that we report in the *KCNJ11* group were mutation specific; the two individuals with the R201H mutation had no overt features and only some subtle abnormalities on neuropsychological testing (Supplementary Table 2). As a result, both were able to live independently and support themselves financially. Those with more severe features required high levels of support from family members and professionals in health care, education, and social care. This is consistent with previous studies showing that the severity of the CNS phenotype is related to the specific mutation; for example, the V59M mutation results in more severe features, greater impairment in daily living skills (13), and greater impact on families (16). Interestingly, however, there was a relatively good level of social integration from all patients with *KCNJ11* mutations even when the neurobehavioral features were severe.

Some of our findings contrast with previous research. To our knowledge, choreiform movements have not previously been associated with *KCNJ11* PNDM but were observed in one individual with the V59M mutation in our study. We did not identify abnormal tone in our cohort, which contrasts with the hypotonia previously reported, particularly in the context of DEND/iDEND syndrome (42). This may be explained by seven of eight individuals in our study being sulfonylurea treated; improvement in tone to near normal following transfer from insulin to sulfonylureas has been observed in a recent study of children with *KCNJ11* PNDM (23). Similarly, improvement of visuospatial abilities and attention following transfer to sulfonylureas was noted in the pediatric study (23), which could account for the attention deficits and visuospatial impairment being less marked in our cohort of sulfonylurea-treated adults than might have been expected given previous descriptions (17,23). Our neuroimaging findings contrast with this pediatric study in which there were nonspecific findings in 12 of 17 who underwent brain MRI, largely comprising white matter abnormalities (23). However, these scans were performed at baseline prior to transfer to sulfonylureas (23). It is not known whether the abnormalities would have improved after a period of sulfonylurea treatment, as has been shown in SPECT studies (24,27).

Sulfonylurea treatment may influence the CNS phenotype in *KCNJ11* PNDM. Two studies have suggested that an earlier age of initiation of sulfonylureas can lead to better CNS outcomes (17,23). We were unable to assess this in our study because median age at transfer to sulfonylureas was 18 years (range 11–34). However, the persistence of CNS features in some patients even after early initiation of treatment (16,23) suggests that other factors are involved. Specifically, active transport of glyburide out of the brain across the blood-brain barrier, as has been demonstrated in a rodent model (28), may result in suboptimal concentrations in the CSF, thereby limiting therapeutic efficacy in the human CNS. Anecdotal clinical experience suggests that this can be partially addressed by increasing the dose of glyburide to ~1 mg/kg/day; however, there have been no cases of complete resolution of CNS features in a patient with iDEND. Another possible reason for the partial response is that pathways that can fully restore K_{ATP} channel function in other tissues are not available in the CNS to interact with brain K_{ATP} channels. For example, restoration of pancreatic K_{ATP} channel function resulting in excellent glycemic control with sulfonylurea treatment is dependent on the activity of incretin hormones (3). Furthermore, there is a theoretical impact of insulin deficiency in utero or C-peptide deficiency prior to sulfonylurea transfer on the brain as an indirect consequence of *KCNJ11* mutations, but more studies are needed to explore this in humans. Indeed, given the complexities of human neurodevelopmental processes, it is likely that several factors contribute in some way to the response of CNS features to sulfonylureas in *KCNJ11* PNDM.

Strengths, Limitations, and Future Work

This study has important strengths. It is the first to assess in detail the CNS manifestations of *KCNJ11* mutations in adults and to control for the nonspecific effects of PNDM by comparing the features in individuals with *INS* mutations. Limitations of the study, which relate to the rarity of the disease, are the small number of individuals in each group, the broad range of mutations studied, and the variable timing of initiation and duration of treatment with sulfonylureas in the *KCNJ11* group. Studies in larger cohorts with single specific mutations would be valuable. Furthermore, exploration of the impact of treatment-specific factors, such as age of initiation, dose, and CNS handling of sulfonylureas in humans, on CNS features in *KCNJ11* PNDM is warranted.

Conclusion

The CNS phenotype in adults with *KCNJ11* mutations comprises learning difficulty, autistic features, subtle motor dysfunction, moderately reduced IQ, and impaired attention, perceptual reasoning, and working memory. The severity of these features varies with the causative mutation. They persist despite long-term sulfonylurea therapy, at least when this is started after the first decade of life, and represent the major burden from *KCNJ11* mutations once glycemia is well controlled on sulfonylureas. These CNS features are not present in individuals with *INS* mutations, which indicates that they occur not as a result of the lifelong metabolic disturbance imposed by PNDM but, rather, as a consequence of impaired K_{ATP} channel function in the brain. Clinicians in adult and pediatric medicine should be aware of the potential impact of CNS features in patients with *KCNJ11* mutations and should consider multidisciplinary management to ensure appropriate support is provided.

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