



Long-term Follow-up of Glycemic and Neurological Outcomes in an International Series of Patients With Sulfonylurea-Treated *ABCC8* Permanent Neonatal Diabetes

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OBJECTIVE

ABCC8 mutations cause neonatal diabetes mellitus that can be transient (TNDM) or, less commonly, permanent (PNDM); ~90% of individuals can be treated with oral sulfonylureas instead of insulin. Previous studies suggested that people with *ABCC8*-PNDM require lower sulfonylurea doses and have milder neurological features than those with *KCNJ11*-PNDM. However, these studies were short-term and included combinations of *ABCC8*-PNDM and *ABCC8*-TNDM. We aimed to assess the long-term glycemic and neurological outcomes in sulfonylurea-treated *ABCC8*-PNDM.

RESEARCH DESIGN AND METHODS

We studied all 24 individuals with *ABCC8*-PNDM diagnosed in the U.K., Italy, France, and U.S. known to transfer from insulin to sulfonylureas before May 2010. Data on glycemic control, sulfonylurea dose, adverse effects including hypoglycemia, and neurological features were analyzed using nonparametric statistical methods.

RESULTS

Long-term data were obtained for 21 of 24 individuals (median follow-up 10.0 [range 4.1–13.2] years). Eighteen of 21 remained on sulfonylureas without insulin at the most recent follow-up. Glycemic control improved on sulfonylureas (presulfonylurea vs. 1-year posttransfer HbA_{1c} 7.2% vs. 5.7%, $P = 0.0004$) and remained excellent long-term (1-year vs. 10-year HbA_{1c} 5.7% vs. 6.5%, $P = 0.04$), $n = 16$. Relatively high doses were used (1-year vs. 10-year dose 0.37 vs. 0.25 mg/kg/day glyburide, $P = 0.50$) without any severe hypoglycemia. Neurological features were reported in 13 of 21 individuals; these improved following sulfonylurea transfer in 7 of 13. The most common features were learning difficulties (52%), developmental delay (48%), and attention deficit hyperactivity disorder (38%).

CONCLUSIONS

Sulfonylurea treatment of *ABCC8*-PNDM results in excellent long-term glycemic control. Overt neurological features frequently occur and may improve with sulfonylureas, supporting early, rapid genetic testing to guide appropriate treatment and neurodevelopmental assessment.

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The *ABCC8* gene encodes the SUR1 subunit of the pancreatic ATP-sensitive potassium (K_{ATP}) channel (1). SUR1 forms hetero-octameric complexes with Kir6.2, encoded by the *KCNJ11* gene (2). Mutations in K_{ATP} channel genes are the most common cause of neonatal diabetes mellitus (NDM) in nonconsanguineous populations, with ~15–20% as a result of *ABCC8* mutations and ~25–30% as a result of *KCNJ11* mutations (3). NDM typically occurs in the first 6 months of life and can be permanent (PNDM), where diabetes persists lifelong, or transient (TNDM), where there is a period of remission of diabetes after 6–12 months followed by relapse in adolescence or early adulthood (4). *ABCC8* mutations cause TNDM in ~80% of cases and PNDM in ~20%; the opposite pattern is observed with *KCNJ11* mutations, which most frequently result in PNDM (5).

ABCC8 and *KCNJ11* mutations cause NDM by preventing closure of pancreatic K_{ATP} channels in response to rising glucose (6,7). This results in insulin deficiency, which historically has required treatment with replacement doses of insulin. However, in ~90% of affected individuals, sulfonylurea treatment can bypass the genetic defect by binding SUR1 and closing pancreatic K_{ATP} channels, promoting secretion of endogenous insulin and allowing patients to stop insulin injections and achieve excellent glycemic control and better quality of life (8–10). Sulfonylureas are the optimum treatment for *KCNJ11*-PNDM long term; in patients who successfully transfer from insulin to sulfonylureas, metabolic control is maintained in >90% for at least 10 years with no serious adverse effects, despite doses being ~2–10 times higher than those recommended in type 2 diabetes (11). Short-term studies have suggested that lower doses of sulfonylurea are required to treat *ABCC8*-NDM compared with *KCNJ11*-NDM (9,12). However, many studies have comprised individuals with *ABCC8*-PNDM and with *ABCC8*-TNDM, which have different clinical courses and treatment requirements (5,6,9). No study has assessed the long-term outcomes of sulfonylurea treatment specifically in *ABCC8*-PNDM.

ABCC8 and *KCNJ11* are both expressed in the brain as well as in the pancreas (13,14); therefore, in addition to diabetes, central nervous system (CNS) features are observed in individuals with

K_{ATP} channel mutations. These vary from the severe DEND syndrome (developmental delay [DD], epilepsy, and NDM) to mild neuropsychological impairments detectable only on detailed neuropsychomotor testing (5,15). In *KCNJ11*-PNDM, there is some correlation between the position of the variant in the protein and the clinical features. In contrast, in *ABCC8*-PNDM, genotype-phenotype relationships appear less distinct (16). In around one-half of individuals with *KCNJ11*-PNDM, sulfonylurea treatment results in partial improvement of the neurological features, which is believed to be due to the action of glyburide on K_{ATP} channels in the brain (11,17).

Observational studies have suggested that the CNS features are not as common and/or severe in individuals with *ABCC8* mutations (5,6,18,19) compared with those with *KCNJ11* mutations. However, as discussed above, previous research findings are based on cohorts containing both individuals with *ABCC8*-PNDM and individuals with *ABCC8*-TNDM. In addition, the majority of studies that have investigated the neurodevelopmental features associated with K_{ATP} channel mutations and the response of these features to sulfonylurea treatment focused on patients with *KCNJ11*-PNDM.

Research related to the CNS features in individuals with *ABCC8*-PNDM and the impact of long-term sulfonylurea treatment on both glycemic and neurological outcomes is crucial to establish and inform clinical guidelines for this specific subtype. The aim of this study was to assess the long-term glycemic and neurological response to sulfonylureas in an international cohort of patients with PNDM as a result of *ABCC8* mutations.

RESEARCH DESIGN AND METHODS

Patient Cohort

Patients with a molecular genetic diagnosis of PNDM as a result of mutations in the *ABCC8* gene (NM_001287174.1) confirmed in laboratories in Exeter, Rome, Paris, and Chicago known to transfer to sulfonylureas before 30 April 2010 with no period of remission of their diabetes were eligible for inclusion in the study ($n = 24$). Three patients were lost to follow-up in the 1st year after sulfonylurea transfer and were therefore excluded, leaving 21 patients with sufficient follow-up data (>4 years) for further analyses.

The study was conducted in accordance with the Declaration of Helsinki as revised in 2000. Patient data were collected during routine clinical care or through research surveys and were anonymized for use in the study.

Data Collection

Data were collected from the clinical records of participating patients or through research surveys completed by the participant or their carers. Data on glycemic control, sulfonylurea dose, and hypoglycemia were collected before and after transfer from insulin to sulfonylureas and annually until the most recent clinic follow-up. Clinicians and participants were asked to report side effects or diabetes complications that occurred at any time point during the follow-up and, if so, to provide details about these.

Data on neurological features were collected before transfer from insulin to sulfonylureas and after transfer at the most recent follow-up. Clinicians or participants were specifically asked about the presence of DD, learning difficulties (LD), attention deficit hyperactivity disorder, epilepsy, sleep problems, muscle weakness, anxiety, autism, and spasticity as well as about other difficulties (11) and whether these features (if present) had improved on transfer to sulfonylureas.

Statistical Analysis

Data were analyzed with Stata 16.0 software using nonparametric statistical methods. Clinical characteristics of patients who remained on sulfonylureas alone were compared with those who required permanent reintroduction of insulin using the Mann-Whitney test for continuous data and two-sample test of proportions for categorical data. For those patients who remained on sulfonylureas alone for the duration of the follow-up, paired data on metabolic control (HbA_{1c}) and sulfonylurea dose were compared using the Wilcoxon signed rank test. For individuals with annual data available for >50% of time points, longitudinal trends in HbA_{1c} and sulfonylurea dose were plotted. Missing data were imputed as previously described (11).

Individuals who required insulin therapy only transiently or who were prescribed any other oral antidiabetic medication at

any point in the follow-up were classified in the sulfonylurea-only group. One individual (mutation, L1148R/R1380C) transferred from insulin to sulfonylureas twice at age 18 months (for 4 years) and again at age 26 years. His follow-up data relate to the second sulfonylurea transfer because no data were available after the first transfer 35 years ago.

For sulfonylureas other than glyburide, doses were converted to glyburide equivalent using percentage of maximum glibenclamide (glyburide) dose as per the British National Formulary (20). Data are presented as median (range) unless stated otherwise. For all analyses, $P < 0.05$ was used to denote statistical significance.

Data and Resource Availability

The research data supporting this publication are provided within the manuscript and Supplementary Material.

RESULTS

Clinical Characteristics

Clinical characteristics of the patients included in the study are shown in Tables 1 and 2.

Duration of Follow-up

Median duration of follow-up was 10.0 (4.1–13.2) years, comprising a total of 205 patient-years.

Sulfonylurea Efficacy

At most recent follow-up, 18 of 21 (86%) patients remained on sulfonylurea therapy without insulin. For all three individuals who had restarted insulin, clinicians reported problems with adherence with prescribed medication and/or periods of loss to clinic/hospital follow-up. Clinical characteristics were similar between the individuals who remained on sulfonylureas versus those who required reintroduction of insulin (Table 1).

Type of Sulfonylurea Prescribed

All patients who remained independent of insulin at most recent follow-up were prescribed glyburide for the duration of the study. One patient was prescribed glyburide at initial transfer from insulin and was switched to tolbutamide at day 45 posttransfer (21); this individual subsequently required reintroduction of insulin therapy, having stopped sulfonylurea treatment while lost to hospital follow-up.

Metabolic Control and Sulfonylurea Dose

Paired data on pretransfer HbA_{1c} and HbA_{1c} and sulfonylurea dose at year 1 (median 0.97 years, range 0.27–1.76 years) and year 10 (9.8 years, 6.1–12.5 years) were available for 16 individuals. In these individuals, glycemic control improved on transfer to sulfonylurea (pretransfer vs. 1-year HbA_{1c} 7.2% [5.3–9.5%]

Table 1—Clinical features of the whole cohort, including all data available at all time points

Clinical feature	On SU without insulin at most recent follow-up (<i>n</i> = 18)	On insulin with or without SU at most recent follow-up (<i>n</i> = 3)	<i>P</i> value (on SU vs. on insulin)
Genotype	E208K/Y263D, V86G/N, D212I/N, P45L/G1401R, V86A/N, L1295F/N, T229I/V1532L, L225P/N, L135P/N, 2 E382K/E382K, L213R/N, R168C/G1256S, V215A/V215A, E208K/D1472N, V324M/W688R, L213P/N, L1148R/R1380C	D209E/N, R1380L/N, Q211K/N	NA
Male, <i>n</i> (%)	10 (56)	0 (0)	0.07
Birth weight (g)	2,750 (1,510–3,402) (<i>n</i> = 16)	2,700 (2,400–2,700) (<i>n</i> = 3)	0.62
Age			
At diagnosis (weeks)	7.5 (1.0–47.0) (<i>n</i> = 18)	6.0 (5.0–17.0) (<i>n</i> = 3)	1.00
At transfer to SU (years)	7.6 (0.5–26.0) (<i>n</i> = 18)	5.8 (2.8–9.4) (<i>n</i> = 3)	0.46
Current (years)	21 (11–36) (<i>n</i> = 18)	19 (16–22) (<i>n</i> = 3)	0.58
Pre-SU HbA _{1c}			
%	7.5 (5.3–9.5) (<i>n</i> = 18)	6.8 (6.7–7.2) (<i>n</i> = 3)	0.52
mmol/mol	58 (34–80) (<i>n</i> = 18)	51 (50–55) (<i>n</i> = 3)	0.52
Year 1 HbA _{1c}			
%	5.7 (5.0–7.3) (<i>n</i> = 16)	6.8 (6.7–6.9) (<i>n</i> = 2)	0.13
mmol/mol	39 (31–56) (<i>n</i> = 16)	51 (50–52) (<i>n</i> = 2)	0.13
Most recent HbA _{1c}			
%	6.7 (5.3–10.1) (<i>n</i> = 18)	9.8 (5.9–10.3) (<i>n</i> = 3)	0.17
mmol/mol	50 (34–87) (<i>n</i> = 18)	84 (41–89) (<i>n</i> = 3)	0.17
SU dose (mg/kg/day glyburide)			
Year 1	0.37 (0.01–1.25) (<i>n</i> = 16)	0.03 (0.01–0.04) (<i>n</i> = 2)	0.05
Most recent	0.35 (0.03–1.30) (<i>n</i> = 18)	0.74 (0.02–1.45) (<i>n</i> = 2)	1.00
Neurological features (any)	10 (56)	3 (100)	0.15
BMI SDS			
Pre-SU	−0.13 (−0.85 to 1.44) (<i>n</i> = 10)	−0.53 (−1.68 to −0.26) (<i>n</i> = 3)	0.10
Most recent	−0.75 (−3.69 to 1.28) (<i>n</i> = 13)	−1.34 (−1.94 to −0.24) (<i>n</i> = 3)	0.19

Data are median (range) unless otherwise indicated. Year 1 is median duration 0.97 (0.27–1.76) years; data closest to 1 year were used. Most recent duration for SU dose and HbA_{1c} is median 10.0 (4.1–13.2) years. Most recent duration for BMI is 9.8 (4.6–13.2) years (most recent time point at which both height and weight data were available). The number of patients is different for each variable because of differences in amount of available data. Most recent SU dose is different from that reported in the RESULTS section because of paired values for SU dose and HbA_{1c} at all time points being unavailable for three individuals included in the table. NA, not applicable; SDS, SD score; SU, sulfonylurea.

vs. 5.7% [5.0–7.3%] [55 (34–80) vs. 39 (31–56) mmol/mol], $P = 0.0004$) and remained excellent at long-term follow-up (1-year vs. 10-year HbA_{1c} 5.7% [5.0–7.3%] vs. 6.5% [5.3–7.7%] [39 (31–56) vs. 48 (34–61) mmol/mol], $P = 0.04$) (Fig. 1A). High doses of sulfonylurea were used in most individuals (1-year vs. 10-year dose 0.37 [0.01–1.25] vs. 0.25 [0.03–1.30] mg/kg/day glyburide, $P = 0.50$) (Fig. 1B). Only three individuals required doses under 0.1 mg/kg/day glyburide at most recent follow-up. In 11 individuals who had sufficient annual data available, there was a gradual reduction in median sulfonylurea dose per kilogram of body weight over time, despite relatively stable glycemic control (Supplementary Fig. 1).

Side Effects

Diarrhea was reported in two individuals. One individual was diagnosed with irritable bowel syndrome. The second individual, previously reported by Codner et al. (21), experienced transient diarrhea on glyburide; this stopped on

switching to tolbutamide. No other adverse effects of sulfonylurea therapy were reported.

Hypoglycemia

There were no episodes of severe hypoglycemia, defined as losing consciousness or having seizures (22), reported over the course of the follow-up in patients treated with sulfonylurea alone. In one individual on glyburide treatment, an episode was reported whereby the blood glucose remained <4.0 mmol/L even after treatment with fruit juice, and third-party assistance was required. Another individual switched treatment from glyburide to tolbutamide (see above) because of episodes of asymptomatic hypoglycemia on glyburide treatment; these settled on tolbutamide (21).

Diabetes Complications

Microvascular complications occurred in two individuals: One had microalbuminuria, and one had microalbuminuria (normotensive) and proliferative retinopathy

requiring intravitreal injections and photocoagulation as well as mildly elevated LDL treated with a statin medication. These individuals transferred to sulfonylureas at age 10 years and 26 years, respectively (after a short period of sulfonylurea treatment as a child [see above]). There were no macrovascular complications reported over the period of follow-up.

BMI

In 10 individuals who remained independent of insulin and had paired height and weight data available, BMI remained normal (BMI SD score pre-sulfonylurea treatment -0.13 [-0.85 to 1.44] and at most recent follow-up on sulfonylureas -0.29 [-0.99 to 0.94], $P = 0.23$).

CNS Features

Thirteen of 21 (62%) patients were reported to have CNS features before and after transfer to sulfonylureas (Fig. 2 and Supplementary Table 1). The most common features at most recent follow-up

Table 2—Clinical features of individuals with dominantly vs. recessively inherited variants in the *ABCC8* gene

Clinical feature	Dominant heterozygous ($n = 11$)	Recessive (compound heterozygous/homozygous) ($n = 10$)	P value
Genotype	D209E/N, D212I/N, L1295F/N, L135P/N, L213P/N, L213R/N, L225P/N, Q211K/N, R1380L/N, V86G/N, V86A/N	2 E382K/E382K, E208K/D1472N, E208K/Y263D, L1148R/R1380C, P45L/G1401R, R168C/G1256S, T229I/V1532L, V215A/V215A, V324M/W688R	NA
Duration of follow-up (years)	11.2 (7.9–13.2)	9.1 (4.1–12.3)	0.02
Male, n (%)	4 (36)	6 (60)	0.27
Birth weight (g)	2,700 (2,100–3,065) ($n = 9$)	2,750 (1,510–3,402) ($n = 10$)	0.76
Age			
At diagnosis (weeks)	6 (2–17) ($n = 11$)	11 (1–47) ($n = 10$)	0.48
At transfer to SU (years)	5.8 (1.9–12.0) ($n = 11$)	10.3 (0.5–26.0) ($n = 10$)	0.12
Current (years)	19 (15–23) ($n = 11$)	22.5 (11–36) ($n = 10$)	0.08
Pre-SU HbA _{1c} %	6.7 (5.3–7.9) ($n = 11$)	8.1 (5.8–9.5) ($n = 10$)	0.001
mmol/mol	50 (34–63) ($n = 11$)	65 (40–80) ($n = 10$)	0.001
Year 1 HbA _{1c} %	6.0 (5.0–6.9) ($n = 10$)	5.7 (5.0–7.3) ($n = 8$)	0.92
mmol/mol	42 (31–52) ($n = 10$)	39 (31–56) ($n = 8$)	0.92
Most recent HbA _{1c} %	7.0 (5.3–10.3) ($n = 11$)	6.3 (5.3–10.1) ($n = 10$)	0.32
mmol/mol	53 (34–89) ($n = 11$)	45 (34–87) ($n = 10$)	0.32
SU dose (mg/kg/day glyburide)			
Year 1	0.09 (0.01–1.25) ($n = 10$)	0.50 (0.17–1.11) ($n = 8$)	0.08
Most recent	0.36 (0.02–1.45) ($n = 10$)	0.35 (0.10–1.30) ($n = 10$)	0.67
On insulin at recent follow-up, n (%)	3 (27)	0 (0)	0.08
With neurological features any at most recent visit, n (%)	7 (64)	6 (60)	0.85

Data are median (range) unless otherwise indicated. The number of patients is different for each variable because of differences in the amount of available data. NA, not applicable; SU, sulfonylurea.

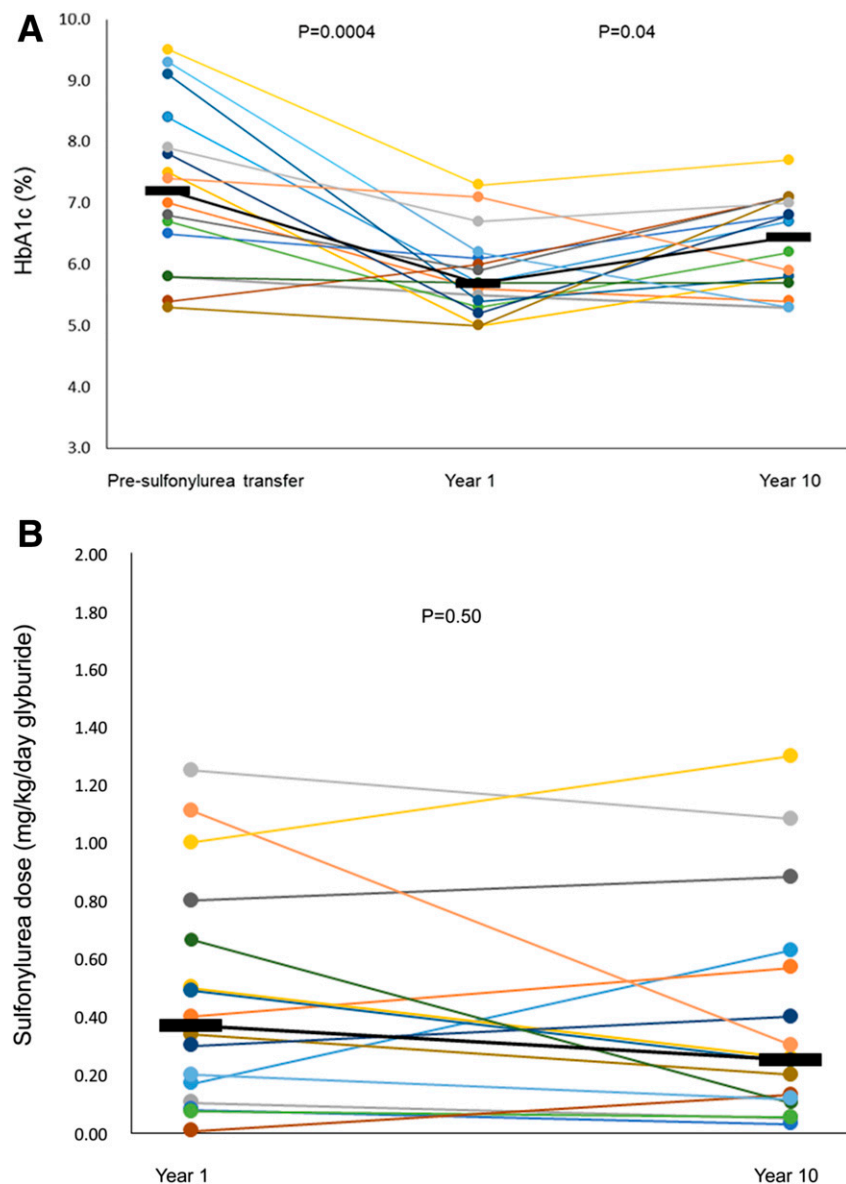


Figure 1—A: HbA_{1c} pre-sulfonyleurea transfer at year 1 and at most recent follow-up in 16 patients with data available at all three time points. Circles represent individuals, and black horizontal lines represent group medians. B: Sulfonyleurea dose at year 1 and at most recent follow-up in 16 patients included in panel A. Circles represent individuals, and black horizontal lines represent group medians.

were DD in 48%, LD in 52%, and attention deficit hyperactivity disorder in 38%. Comorbidity was common: 11 individuals had three or more specific CNS features together. In five individuals, seizures were or may have been a result of factors other than the genetic mutation (Supplementary Table 2).

In 7 of 13 (54%) patients, there was some improvement ($n = 5$) or complete resolution ($n = 2$) noted in neurological features on starting sulfonyleureas (Fig. 2 and Supplementary Table 1). In the two patients whose neurological features completely resolved, both had

DD pretransfer (with LD in one) but subsequently attained a developmental level expected for their age.

All three patients who required reintroduction of insulin treatment had neurological features (Table 1); there was improvement in the electroencephalogram background in one of these patients following initial transfer from insulin onto sulfonyleureas. Age at transfer to sulfonyleureas was similar in patients with and without neurological features at most recent follow-up (6.6 [0.5–18.2] vs. 8.4 [0.9–26.0] years, $P = 0.53$).

CONCLUSIONS

In summary, in our 10-year study of 21 individuals with sulfonyleurea-treated *ABCC8*-PNDM, 86% remained independent of insulin at their most recent follow-up. Furthermore, glycemic control was maintained on relatively high doses of sulfonyleureas, without any reports of severe hypoglycemia or side effects. A large proportion of the cohort (62%) had overt neurological features both before sulfonyleurea transfer and at most recent follow-up, and comorbidity was common. There was partial improvement in some CNS features in just over one-half of individuals following transfer to sulfonyleurea therapy.

The excellent long-term outcomes in sulfonyleurea-treated *ABCC8*-PNDM are similar to those observed in *KCNJ11*-PNDM (11) (Supplementary Table 3). Our data do not support the suggestion from previous studies that lower doses of sulfonyleurea may be required in people with *ABCC8* mutations compared with those with *KCNJ11* mutations (9). This may be due to, at least in part, the inclusion of patients with *ABCC8*-TNDM and *ABCC8*-PNDM in earlier cohort studies (9) and a lower sulfonyleurea dose requirement in the patients with TNDM (23). In this study, behavioral and/or social factors are likely to explain the deterioration in glycemic control in the three individuals with *ABCC8*-PNDM who required reintroduction of insulin.

We have shown that overt CNS features in *ABCC8*-PNDM occur with relatively high frequency and that comorbidity is common, in contrast with previous studies that included cohorts of patients with *ABCC8*-TNDM and *ABCC8*-PNDM (5,6,9). Indeed, the frequency and nature of CNS features in *ABCC8*-PNDM is similar to that observed in *KCNJ11*-PNDM (11) (Supplementary Table 3), with the exception of autism, which has been more frequently reported in *KCNJ11*-PNDM (11,24,25).

The partial improvement in neurological features in 7 of 13 individuals on transferring to sulfonyleureas is consistent with previous cases and suggests that the drugs may improve neurological function in some patients with *ABCC8*-PNDM, although a randomized controlled trial would be required to prove this definitively. It has been suggested

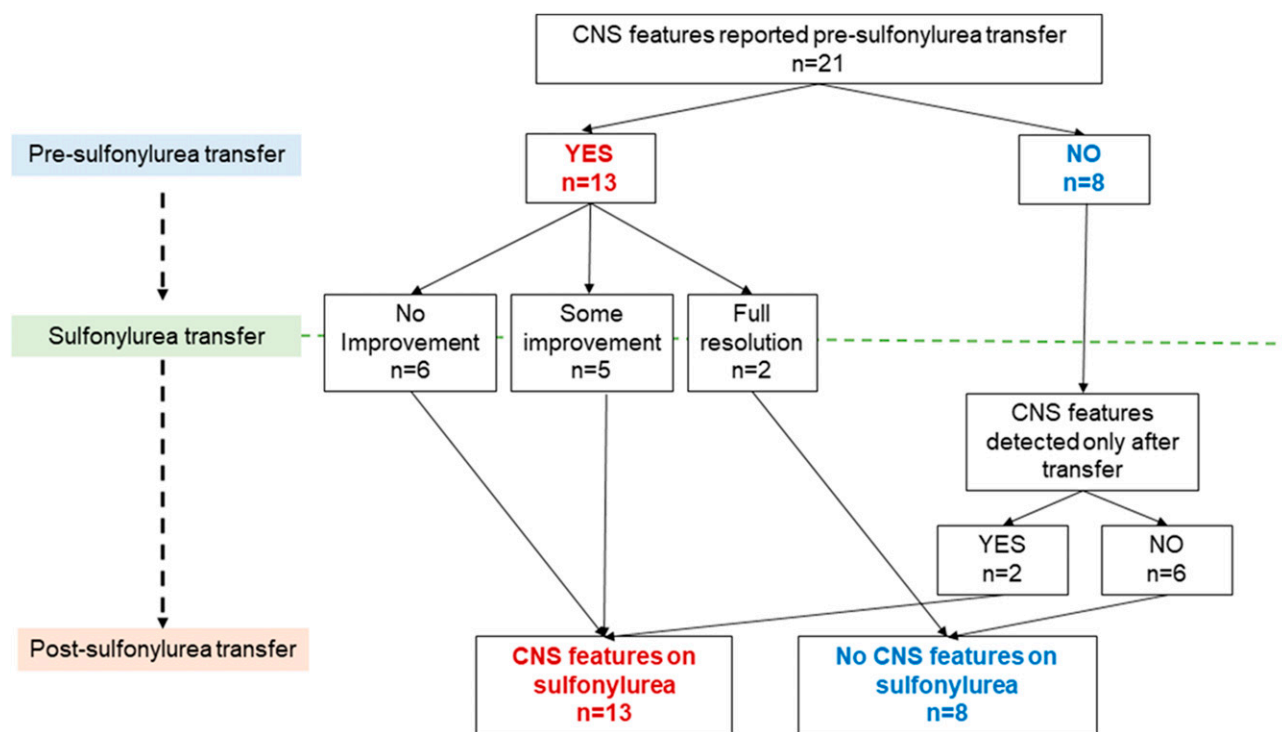


Figure 2—Number of patients with *ABCC8*-PNDM with neurological features relative to sulfonylurea transfer.

that the improvement in neurological features is greater the earlier sulfonylureas are started (17,26), reflecting greater neuroplasticity at a younger age with a so-called sensitive period occurring within the first 6 months of life (27). In our cohort, only two patients transferred under the age of 1 year, and none transferred under the age of 6 months; therefore, this crucial sensitive period for the action of sulfonylureas in the brain may have been missed. Studies in rats have suggested that glyburide is actively transported out of the brain (28); this may make it difficult to achieve therapeutic concentrations of the drug in the cerebrospinal fluid. As a result, recommended doses of glyburide in patients with K_{ATP} channel-related PNDM and severe neurological features are higher (at least ~ 1 mg/kg/day) (29). Of those individuals who remained independent of insulin in our cohort, only two were on a dose this high at their most recent follow-up. Furthermore, there was a tendency for glyburide doses to fall over time, which may reflect lack of adjustment of total daily doses according to increases in body weight as children grow. This may also explain the slightly higher HbA_{1c} at the most recent follow-up when compared with year 1.

These factors emphasize the need for early genetic testing and identification of all patients with *ABCC8*-PNDM. Prompt genetic diagnosis facilitates early transfer to sulfonylureas as well as systematic screening of all affected individuals for neurodevelopmental features at diagnosis and follow-up and provision of appropriate support. Clinicians should consider higher doses of sulfonylureas if neurological features are present. They should also regularly adjust total daily dose to maintain the same dose per kilogram of body weight over time, thereby optimizing treatment for both glycemia and neurological features.

Variable modes of inheritance are observed in our cohort; there is a mixture of dominant heterozygous *ABCC8* mutations ($n = 11$) as well as compound heterozygous ($n = 7$) and homozygous variants ($n = 3$), in keeping with previous studies (30). This has implications for genetic counseling in relation to recurrence risk and carrier status in future offspring, which will be different for dominant versus recessive inheritance. In this study, there were no differences in long-term outcomes between individuals with dominant heterozygous versus recessive (homozygous and compound heterozygous) mutations (Table 2). However, our study was not designed to address

this question, and research in larger cohorts will be required to investigate the impact of mode of inheritance on clinical outcomes in *ABCC8*-PNDM. An additional limitation is the wide range of specific genetic variants included, which prevents the identification of strong genotype-phenotype relationships.

Finally, neurological features were not screened for systematically through repeated assessments in one center over the course of the follow-up, and comprehensive neuropsychological testing was not done as part of this study. Therefore, there is likely to be variable ascertainment and/or reporting of CNS features on the basis of what was recorded in the clinical notes. This might result in an underestimation of the extent of neurological involvement in affected individuals. It is not possible to fully distinguish the relative contributions of mutant K_{ATP} channels in the brain and other factors from the neurological features reported (Supplementary Table 2). It is likely that in at least some individuals, the neurological features will be due to a combination of different etiologies. Despite these limitations, this study is the first to assess the long-term treatment response and CNS features in an international cohort of patients with *ABCC8*-PNDM. Further research in larger

cohorts of individuals with *ABCC8* mutations will be required to investigate in more detail the CNS phenotype, genotype-phenotype relationships, and factors influencing the glycemic response to sulfonylureas (e.g., specific physiological states such as puberty and pregnancy).

In conclusion, we have shown for the first time that sulfonylurea therapy is effective and safe long term for people with PNDM as a result of *ABCC8* mutations, with excellent glycemic control maintained over 10 years without severe hypoglycemia or side effects, despite relatively high doses in most patients. Importantly, affected individuals frequently have multiple overt CNS features, which, in some, may partly improve with sulfonylureas. Rapid genetic diagnosis is crucial to facilitate early initiation of precision therapy with sulfonylureas in *ABCC8*-PNDM and to enable prompt identification of neurodevelopmental features and provision of appropriate support for affected families.

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