

Switching to Sulphonylureas in Children With iDEND Syndrome Caused by *KCNJ11* Mutations Results in Improved Cerebellar Perfusion

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OBJECTIVE—Activating mutations in the *KCNJ11* gene, encoding the Kir6.2 subunit of the K_{ATP} channel, result in permanent neonatal diabetes mellitus. They also may cause neurologic symptoms such as mental retardation and motor problems (iDEND syndrome) and epilepsy (DEND syndrome). Sulphonylurea (SU) treatment is reported to alleviate both the neurologic symptoms and diabetes in such cases. The study aimed to establish the magnitude and functional basis of the effect of SUs on the neurologic phenotype in children with iDEND using neuroimaging before and after insulin replacement with glibenclamide.

RESEARCH DESIGN AND METHODS—To localize and quantify the effect of glibenclamide administration, we performed single-photon emission computed tomography in seven patients with different mutations in *KCNJ11*. In five patients, measurements before and after initiation of SU treatment were performed.

RESULTS—Significant changes in single-photon emission computed tomography signal intensity after transfer to SU therapy were restricted to the cerebellum, consistent with previous data showing high Kir6.2 expression in this brain region. Cerebellar perfusion improved for both left ($P = 0.006$) and right ($P = 0.01$) hemispheres, with the mean improvement being $26.7 \pm 7.1\%$ ($n = 5$). No patients showed deterioration of cerebellar perfusion on SU therapy. Electrophysiological studies revealed a good correlation between the magnitude of K_{ATP} channel dysfunction and the clinical phenotype; mutant channels with the greatest reduction in adenosine 5'-triphosphate inhibition were associated with the most severe neurologic symptoms.

CONCLUSIONS—We conclude it is likely that at least some of the beneficial effects of SU treatment on neurodevelopment in iDEND patients result from improved cerebellar perfusion.

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Approximately 50% of cases of permanent neonatal diabetes mellitus are caused by mutations in the genes encoding either the pore-forming (Kir6.2, *KCNJ11*) or regulatory (SUR1, *ABCC8*) subunits of the ATP-sensitive K^+ (K_{ATP}) channel (1). In some patients with these mutations, neurologic symptoms such as mental retardation, impaired motor development, and

hypotonia coexist with neonatal diabetes (iDEND syndrome); if epilepsy is also present, then the condition is called DEND syndrome (2). Previous studies have shown that it is possible to alleviate diabetes and some of the neurologic symptoms by substituting insulin therapy with orally ingested sulphonylurea (SU) drugs (3). In one patient, the improvement in neurologic function was associated with enhanced perfusion of the brain, particularly of the cerebellum, as measured by single-photon emission computed tomography (SPECT). To determine if this effect is common to patients treated with SU, we performed SPECT in patients with different mutations in *KCNJ11* and varying clinical phenotypes.

RESEARCH DESIGN AND METHODS

The Ethics Committee of the Medical University of Lodz approved the project. Parents of participants gave written informed consent for participation of their children in the study.

The study group consisted of seven patients (four boys and three girls) with gain-of-function mutations of the *KCNJ11* gene who were recruited to the Polish Registry of Monogenic Diabetes (The TEAM project). Their clinical characteristics are presented in Table 1. All patients transferred successfully to SU and showed improved blood glucose levels (4). The age of the patients at the time of transfer ranged from 5 to 21 years.

Mental and motor development

Rudimentary neurologic testing was performed for all patients before and after introduction of SU therapy, as described previously (3). Briefly, an assessment of mental and motor function was performed using medical records of developmental milestones during infancy and up to the age of 2 years. The Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R) was used to assess mental development. Attention deficit hyperactivity disorder was diagnosed

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Table 1—Clinical characteristics of the study group

Patient ID	KCNJ11 mutation	Sex	Neurologic features	Age at diabetes diagnosis (weeks)	Age at SU introduction and the first SPECT examination (years)	HbA _{1c} level at introduction and the first SPECT examination (%)	Effective daily dose of SU (mg/kg)	Time to the second SPECT examination after SU introduction (months)	HbA _{1c} level at the second SPECT examination (%)
Pol23	H46L	F	iDEND	12	6.2	6.7	0.8	5	5.9
Pol32	G53D	M	iDEND	3	17.2	7.2	1.0 + glargine 10 IU/day	NA	NA
Pol45	G53D (Pr2)	F	iDEND	16	7.9	8.3	1.0	5	7.3
Pol16	V59M	M	iDEND	16	4.5	6.7	1.1	5.8	6.1
Pol41	R50Q	M	Negative	20	14.0	6.3	0.12*	5.8	5.2
Pol33	R201H	F	Negative	12	8.2	7.1	0.5	6.2	6.5
Pol31†	E229K	M	Negative	6	10.5	7.1	0.15*	5.5	6.7

The SUs used were glibenclamide or glipizide (gastrointestinal therapeutic system [GITS]—extended release). SU therapy was started and titrated to the therapeutic level according to published protocols (15). NA, not available. *Glipizide GITS dose; †SPECT performed only after SU introduction.

according to criteria provided in the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual*. Electroencephalography (EEG) was performed using 32-channel digital EEG equipment (ELMIKO, Warsaw, Poland), but only before SU therapy. For recording, viewing, analysis, and archiving of EEG records, ELMIKO DigiTrack (ELMIKO, Warsaw, Poland) software was applied. The records were analyzed by a neurophysiologist and verified by the consultant in pediatric neurology.

SPECT studies

Imaging studies were performed twice (before and 6 months after switching from insulin to SU) in five individuals with the following mutations: H46 L (3), R201H, R50Q, G53D, and V59M. One patient with a G53D mutation was examined only before transfer to SU and the patient with an E229 K mutation was only available after transfer.

SPECT studies of brain perfusion were performed according to the European Association of Nuclear Medicine procedure guidelines for brain perfusion SPECT using technetium 99m (^{99m}Tc)-labeled radiopharmaceuticals version 2 (5) after intravenous injection of ^{99m}Tc ethyl cysteine dimer under resting conditions. SPECT scanning was performed using a dual-head γ camera Infinia Hawkeye (GE Medical System) with a dedicated computer workstation (Xeleris). Examinations were assessed by two independent experienced nuclear medicine reviewers (M.G., M.Bi.) in triplicate to minimize the risk of intraobserver and interobserver bias. The NeuroGam, an application licensed by Segami Corporation, was used for qualitative and quantitative voxel analyses of brain perfusion in respective regions of interest. These were performed separately for left and right hemispheres. The serum glucose level was measured before and after SPECT examination (range, 4.9–5.9 mmol/L). For all SPECT examinations, the patients were administered total intravenous anesthesia using ketamine. This was dictated by the fact that four of the patients were younger than age 9 years, patient Pol32 had severe mental retardation, and patient Pol23 had attention deficit hyperactivity disorder diagnosed. Therefore, to reduce any variability attributable to patient anxiety or lack of cooperation, we obtained Bioethics Committee approval to perform these studies under short-term intravenous general anesthesia, including

approval for collaborative patients older than 9 years of age to unify conditions of the study. Both examinations were performed ~1 h after intravenous injection of ^{99m}Tc -ethyl cysteine dimer under resting conditions. To eliminate possible anatomical variability, we performed simultaneous magnetic resonance imaging examination and SPECT/magnetic resonance imaging digital fusion of images. We compared individual density counts for all regions of interest and, to make our results comparable with the reference range in children (6), we computed cerebro-cerebellar indexes by dividing density counts of particular regions by those of the cerebellum.

Comparisons were made with the Mann-Whitney *U* test with a Benjamini-Hochberg procedure used for false discovery rate computation to correct for multiple hypothesis testing.

Electrophysiological studies

Human Kir6.2 (Genbank NM000525; E23 and I337) and rat SUR1 (Genbank L40624) were used. Site-directed mutagenesis, synthesis of capped mRNA, and preparation and culture of *Xenopus laevis* oocytes were performed as previously reported (7). Oocytes were coinjected with ~4 ng of SUR1 mRNA and ~0.8 ng of wild-type (WT) or mutant Kir6.2-G53D mRNA and studied 1–4 days after injection.

Whole-cell (WC) currents were recorded using a two-electrode voltage-clamp in response to voltage steps of ± 20 mV from a holding potential of -10 mV in a solution containing the following (mmol/L): 90 KCl, 1 MgCl_2 , 1.8 CaCl_2 , and 5 HEPES (pH 7.4 with KOH). Metabolic inhibition was induced by 3 mmol/L Na-azide. Tolbutamide (0.5 mmol/L) was used to block K_{ATP} channels.

ATP sensitivity was measured in inside-out patches at -60 mV. The pipette (external) solution contained the following (mmol/L): 140 KCl, 1.2 MgCl_2 , 2.6 CaCl_2 , and 10 HEPES (pH 7.4 with KOH). The intracellular solution contained the following (mmol/L): 107 KCl, 11 EGTA, 2 MgCl_2 , 1 CaCl_2 , 10 HEPES (pH 7.2 with KOH), and MgATP as indicated. Control solutions were alternated with test (ATP-containing) solutions and current (*I*) is expressed as a fraction of the mean of that in control solution (I_c) before and after ATP application. ATP concentration-response curves were fit to the following: $I/I_c = 1/[1 + ([\text{ATP}]/\text{IC}_{50})^h]$, where [ATP] is the ATP concentration, IC_{50} is the ATP concentration at which

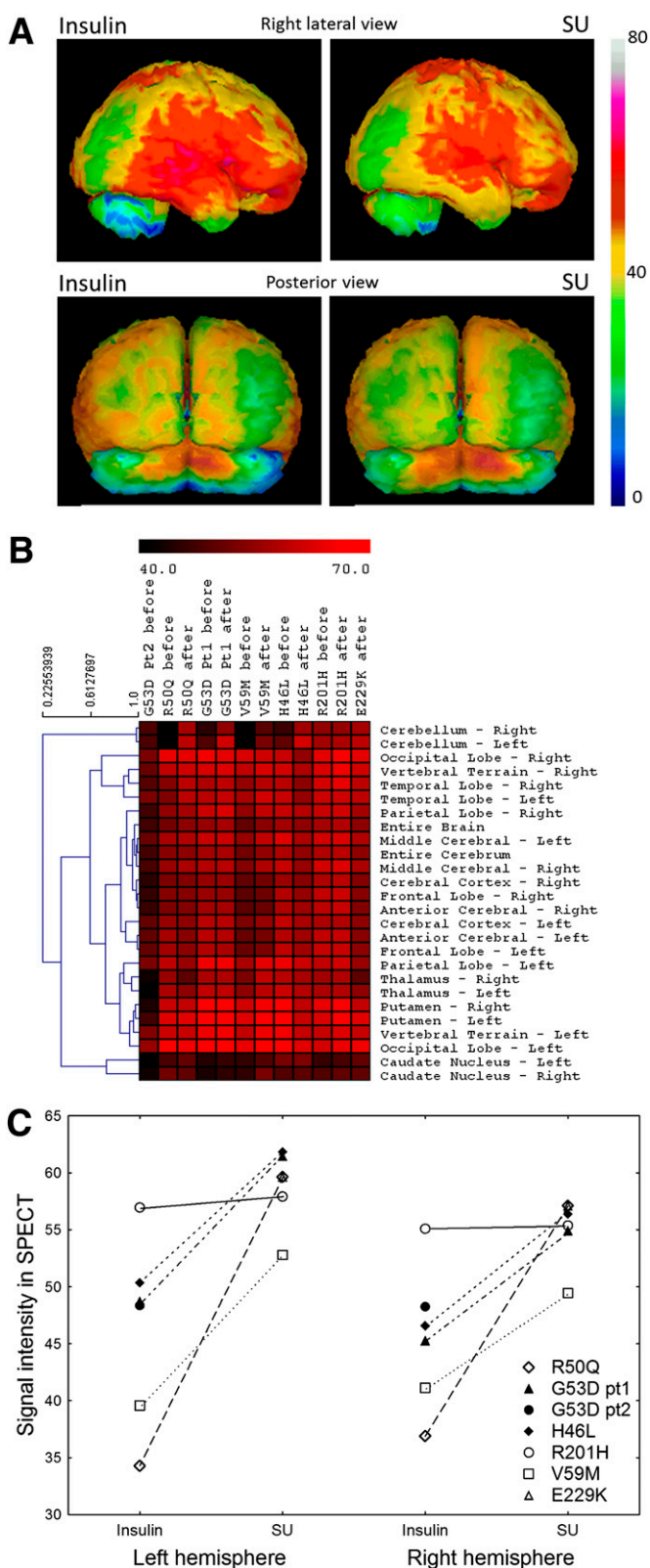


Figure 1—A: Representative SPECT scans of brain perfusion paired during insulin and SU therapy for the patient with a V59M substitution in Kir6.2 (NeuroGam software). B: Hierarchical clustering heat map for average signal intensity in the indicated brain regions for patients with the specified mutations before and after transfer to SU therapy. Brighter red represents increased ^{99m}Tc -ethyl cysteine dimer uptake corresponding to augmented perfusion. Pearson correlation coefficients were used as distance measurements in this analysis and are shown as a dendrogram on the left side of the heat map. C: Mean SPECT signal intensity in the left and right hemispheres of the cerebellum before and after initiation of SU treatment.

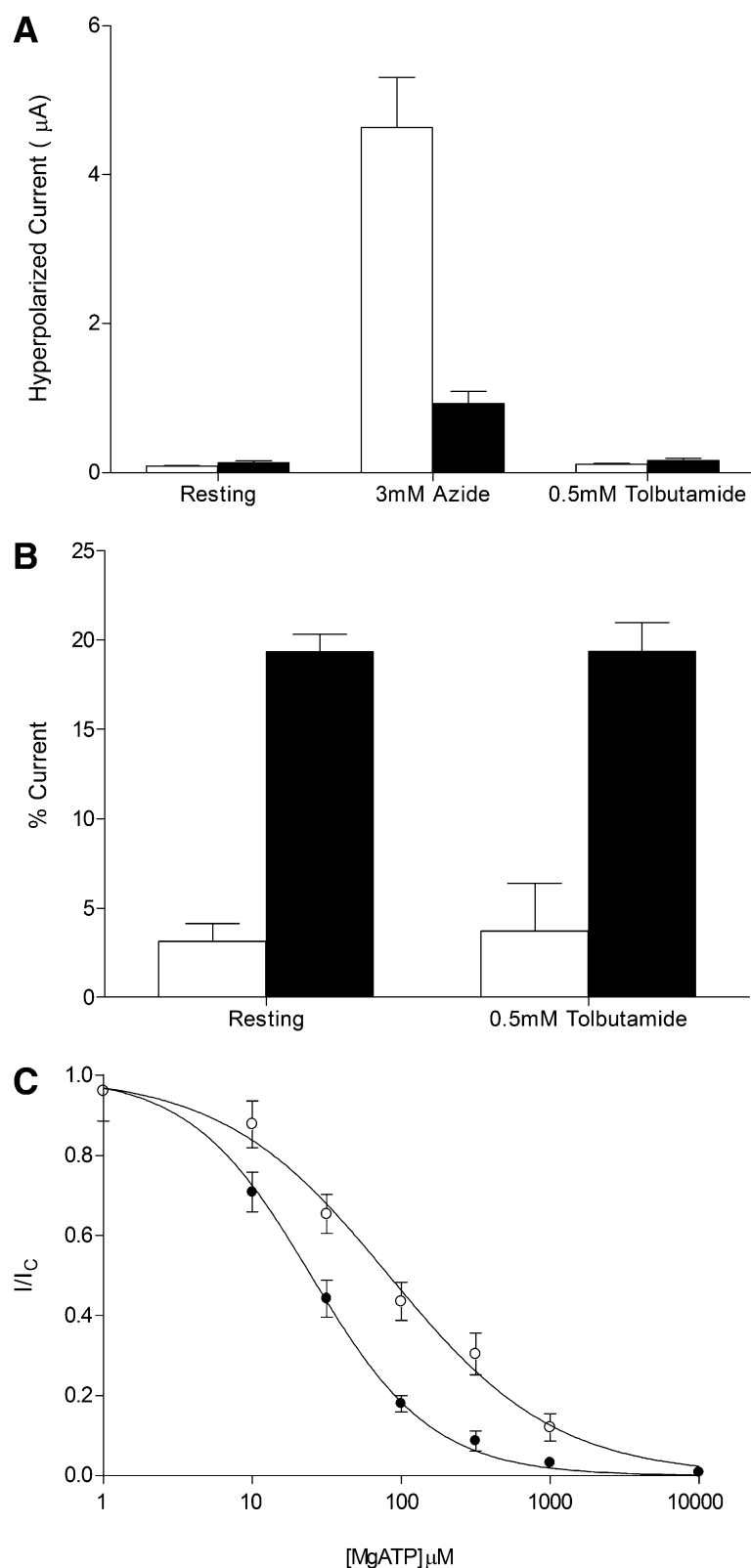


Figure 2—A: Mean \pm SEM for steady-state WC K_{ATP} currents evoked by a voltage step from -10 to -30 mV before (resting) and after application of 3 mmol/L Na-azide, and after application of 0.5 mmol/L tolbutamide (Tolb) for oocytes injected with Kir6.2 (white; $n = 12$) or a 1:1 mixture of Kir6.2 and Kir6.2-G53D (black; $n = 24$) mRNA, plus SUR1 mRNA. B: Mean \pm SEM for WC K_{ATP} currents evoked by a voltage step from -10 to -30 mV under resting conditions and after application of 0.5 mmol/L Tolb for oocytes injected with Kir6.2 (white; $n = 12$) or a 1:1 mixture of Kir6.2 and Kir6.2-G53D (black; $n = 24$) mRNA, plus SUR1 mRNA. Currents are expressed as

inhibition is half maximal, and h is the slope factor.

RESULTS

Clinical evaluation

All patients had *KCNJ11* mutations, with four patients being classified as having iDEND and three as having permanent neonatal diabetes mellitus. All patients had normal EEG recordings. None of the permanent neonatal diabetes mellitus patients had neurologic features. Among iDEND children, one patient (Pol23) had attention deficit hyperactivity disorder and mild mental retardation diagnosed, one (Pol32) had moderate mental retardation and severe motor disability, and two patients had only mild mental retardation. Only one (Pol23) showed significant improvement in mental and motor function with SU therapy. This patient has been described previously (3).

SPECT studies

Figure 1A shows representative SPECT scans from the same iDEND patient, first when treated with insulin and then subsequently treated with SU.

Average scores of signal intensity for respective brain regions of interest in all tested patients were computed and subjected to hierarchical clustering using Spearman r coefficient as a distance measure. Changes in regional perfusion are shown in Fig. 1A–C and in the Supplementary Table 1. Significant changes in signal intensity after transfer to SU therapy were restricted to the cerebellum. A marked improvement in paired observation comparisons for cerebellar perfusion was observed in all cases except for the patient with the R201H mutation (8). The signal intensity was significantly higher for both the left ($P = 0.006$; false discovery rate, 0.13) and right ($P = 0.01$; false discovery rate, 0.13) cerebral hemisphere after introduction of SU treatment (Fig. 1A–C). The mean improvement was $26.7 \pm 7.14\%$ ($n = 5$). No patients showed deterioration of cerebellar perfusion with SU therapy. The mean signal change in all other regions did not exceed the range of -1.5 to 4.5% in signal intensity variation (Supplementary Table 1), which was within the range of intraindividual variability (5.96 and 7.20%, depending on the assessing radiologist) and the range of assessor-dependent variability (4.55%). As scores for the cerebellum increased because of SU treatment, the cerebro-cerebellar indexes proportionally

Table 2—Electrophysiological data for K_{ATP} channels carrying the indicated mutation in Kir6.2 (KCNJ11) studied in the heterozygous state

Mutation	IC ₅₀ μ mol/L (MgATP)	Current at 3 mmol/L MgATP as a percentage of that in the absence of MgATP	Percent block of WC current by 0.5 mmol/L tolbutamide	Resting WC current as a percentage of that in 3 mmol/L azide	Fold increase in resting WC current compared with WT	Reference
H46L	544 \pm 157	17 \pm 3	87 \pm 3	55	18	Mlynarski (3)
R50Q	128 \pm 16	8.2 \pm 0.8	89 \pm 4	7	2	Shimomura (17)
V59M	44 \pm 7	13	81 \pm 1	17 \pm 7	5	Proks (18)
R201H	143 \pm 25	8	As WT	8.5	3	Proks (18)
E229K	82 \pm 13	3.7 \pm 1.5	95	3.5	—	Girard (16)
G53D	102 \pm 22 (n = 10)	5.7 \pm 1.3 (n = 10)	81 \pm 3 (n = 24)	19 \pm 2 (n = 24)	6	This study
WT	29 \pm 5 (n = 16)	1.1 \pm 0.3 (n = 6)	97 \pm 1 (n = 12)	3 \pm 1 (n = 12)	—	This study

Data on previously reported mutations (3,16–18) are provided for comparative purposes with experimental data on G53D and WT channels. The IC₅₀ and current remaining at 3 mmol/L MgATP were measured in inside-out patches. Other measurements are from WC currents. IC₅₀, half-maximal inhibitory concentration.

decreased, reaching normal reference values for children 4–15 years of age (Supplementary Table 2).

Electrophysiological parameter correlations

We also compared the effect of the patients' mutations on K_{ATP} channel inhibition by ATP and metabolism. Because all patients are heterozygotes, we simulated the heterozygous state by coexpressing SUR1 with a 1:1 mixture of WT and mutant Kir6.2. For each mutation, we measured the magnitude of the WC K_{ATP} current at rest after activation by the metabolic inhibitor azide and inhibition by the SU tolbutamide. We also measured the ATP concentration–inhibition relationship. Figure 2A–C shows data obtained for the Kir6.2-G53D mutation and Table 2 gives the mean data for WT channels and all mutant channels. All mutations increased the IC₅₀ for ATP inhibition and the current magnitude in the presence of 3 mmol/L MgATP (a physiological concentration); the greatest reduction in ATP block was found for the iDEND mutation H46L. The magnitude of the WC current in the absence of metabolic inhibition correlated with the clinical phenotype; the largest currents were found for the most clinically severe mutations. These mutations also showed a lower degree of tolbutamide block.

CONCLUSIONS—It is clear that the mutations that cause the most severe neurologic phenotype are those that

show the largest resting WC K_{ATP} currents. In order of functional severity, the mutations were as follows: H46L > G53D ~ V59M > R50Q ~ R210H ~ E229 K > WT. Patients with least severe mutations (R50Q, R201H, and E229 K) did not show neurologic symptoms.

The most pronounced changes in brain blood flow resulting from transfer from insulin to SU treatment were observed in the cerebellum. All patients (with the exception of the one carrying the R210H mutation) showed an increase in cerebellar perfusion. The R201H patient had the highest cerebellar perfusion initially and this did not change after transfer to glibenclamide; this pattern might be expected because this mutation is not a severe one. The G53D, V59M, and H46 L mutations all cause neurologic problems, and patients with these mutations had a lower initial cerebellar perfusion with insulin, which increased to approximately the same level as for the R201H patient when administered SU. This is consistent with the fact that they cause a more severe phenotype and therefore might be expected to cause worse perfusion with insulin therapy than the R201H mutation.

The patient with R50Q mutation showed unexpected results. Despite the absence of neurologic symptoms and only a moderate impairment of channel function, the SPECT signal intensity with insulin therapy was the lowest and it showed the largest increase. It is possible that other confounding factors may influence cerebellar perfusion in this in-

dividual, but this remains to be determined.

In pancreatic β cells, an increased K_{ATP} current would lead to membrane hyperpolarization and inhibition of insulin secretion. In neurons, it is expected to result in reduced electrical activity. All currents were strongly blocked by tolbutamide, suggesting that if SU is able to cross the blood–brain barrier, then it should close mutant K_{ATP} channels. The large changes in cerebellar perfusion are consistent with the fact that Kir6.2 is strongly expressed within the cerebellum (9). Furthermore, when the V59M gain-of-function mutation was selectively expressed in neurones in a genetically modified mouse model, the electrical activity of cerebellar Purkinje cells was impaired (10). These mice also showed motor problems, including impaired balance and coordination, as predicted if cerebellar function was impaired. Purkinje cell electrical activity in brain slices from these mice was fully restored by a high dose of the SU tolbutamide (10).

A key question is the extent to which SU is able to target brain neurons in vivo. The increase in SPECT signal that we observed in patients treated with glibenclamide suggests the drug may be able to cross the blood–brain barrier, at least to some extent. We propose that glibenclamide closes K_{ATP} channels in cerebellar neurons, thereby stimulating electrical activity, which in turn leads to an increase in blood flow and SPECT signal intensity.

Neurologic improvement observed in patients with *KCNJ11* mutations treated with SU manifests as improved motor function (11–13) and, in some cases, ameliorated cognitive function (3,14). Our finding of increased cerebellar perfusion in all patients after SU therapy could explain the previously reported improvements

a percentage of the maximum current evoked by application of 3 mmol/L azide. C: Mean \pm SEM for relationships between [ATP] and K_{ATP} current (I), expressed relative to that in the absence of nucleotide (I_c), for Kir6.2/SUR1 (WT, open circles, n = 16), and hetKir6.2-G53D/SUR1 (hetG53D, closed circles; n = 10) channels in the presence of Mg²⁺. The lines are drawn to equation 1, with the following parameters: WT (IC₅₀ = 25 μ mol/L, h = 1.1) and hetG53D (IC₅₀ = 83 μ mol/L, h = 0.8).

of motor function in glibenclamide-treated patients (3,11–14). Because all patients were walking before insulin replacement and detailed neurologic testing was not performed before transfer, we could not quantify the extent of motor improvement. Despite the observed benefits, it should be noted that the long-term clinical consequences of this therapy remain unknown and the patients will require further follow-up evaluation.

Because SPECT examinations were performed under short-term anesthesia with ketamine, there was a slight risk that this drug affected the results of the study. However, because we focused on an individual patient's change in perfusion and the same kind of anesthesia was used on both occasions, we think it is unlikely that ketamine would influence the observed amelioration in cerebellum perfusion. No data are available that would suggest children with *KCNJ11* mutations exhibit a different reaction to ketamine than healthy children, suggesting a disease-specific bias also is not likely.

Although our study has several limitations such as a small sample size (reflecting the rarity of this disease) and the lack of objectively quantified motor performance in these patients, we believe that both the neuroimaging and electrophysiological studies shown in this study support the hypothesis of a cerebellum-related effect of SU in iDEND.

In view of clinically confirmed improvement in neurologic function (3) and the beneficial changes we observed in imaging studies, we conclude that SU treatment in patients with iDEND syndrome caused by *KCNJ11* mutations may exert a beneficial effect on the developing brain and may improve cerebellar perfusion.

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I.P. and M.T.M. collected and verified the clinical data in the study centers. M.F.B., C.L., and F.M.A. designed, performed, and analyzed the electrophysiological studies. M.G. and M.Bi. performed imaging studies. I.D. and M.Bo. performed genetic laboratory studies and contributed to discussion. F.M.A. contributed to the writing of the manuscript. W.M.M. designed the study, verified statistical analysis, and wrote the final version of the manuscript. W.M.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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