Sulfonylurea Therapy Benefits Neurological and Psychomotor Functions in Patients With Neonatal Diabetes Owing to Potassium Channel Mutations

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OBJECTIVE

Neonatal diabetes secondary to mutations in potassium-channel subunits is a rare disease but constitutes a paradigm for personalized genetics-based medicine, as replacing the historical treatment with insulin injections with oral sulfonylurea (SU) therapy has been proven beneficial. SU receptors are widely expressed in the brain, and we therefore evaluated potential effects of SU on neurodevelopmental parameters, which are known to be unresponsive to insulin.

RESEARCH DESIGN AND METHODS

We conducted a prospective single-center study. Nineteen patients (15 boys aged 0.1–18.5 years) were switched from insulin to SU therapy. MRI was performed at baseline. Before and 6 or 12 months after the switch, patients underwent quantitative neurological and developmental assessments and electrophysiological nerve and muscle testing.

RESULTS

At baseline, hypotonia, deficiencies in gesture conception or realization, and attention disorders were common. SU improved HbA_{1c} levels (median change −1.55% [range −3.8 to 0.1]; $P < 0.0001$), intelligence scores, hypotonia (in 12 of 15 patients), visual attention deficits (in 10 of 13 patients), gross and fine motor skills (in all patients younger than 4 years old), and gesture conception and realization (in 5 of 8 older patients). Electrophysiological muscle and nerve tests were normal. Cerebral MRI at baseline showed lesions in 12 patients, suggesting that the impairments were central in origin.

CONCLUSIONS

SU therapy in neonatal diabetes secondary to mutations in potassium-channel subunits produces measurable improvements in neuropsychomotor impairments, which are greater in younger patients. An early genetic diagnosis should always be made, allowing for a rapid switch to SU.

Neonatal diabetes is a rare condition that develops during the first months of life with an estimated incidence of 1 in 90,000 newborns (1,2). Neonatal diabetes can be permanent or transient, relapsing around puberty after a period of remission. We recently reported that 42% of patients in a large cohort had a heterozygous

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activating mutation in the coding sequences of the *KCNJ11* or *ABCC8* gene (3), both of which encode the Kir6.2 subunit and SUR1 subunit, respectively, of the K_{ATP} channel. In β-cells, this channel induces membrane depolarization, thereby triggering insulin granule exocytosis (4,5). Sulfonylureas (SUs), which are widely used to treat type 2 diabetes, bind specifically to SUR1, closing the K_{ATP} channel via an ATP-independent mechanism and therefore increasing the release of insulin. We and others have shown that SUs are effective when used instead of subcutaneous insulin in children and adults with Kir6.2- or SUR1-activating mutations (5,6). SU therapy provided excellent metabolic control without the hypoglycemic episodes commonly seen with insulin.

Studies have established that ~20% of patients with mutations in K_{ATP} genes have abnormalities of the standard neurological evaluation ranging from mild to severe developmental delay. The concomitant presence of treatment-resistant epilepsy and muscle weakness is known as developmental delay, epilepsy and neonatal diabetes (DEND) syndrome (3,7); intermediate DEND is a less severe phenotype without epilepsy. However, we recently reported that appropriate testing methods detected developmental impairments in >70% of patients with K_{ATP} gene mutations (3). These impairments adversely affect academic performance, social functioning, and quality of life. They might be improved by SU therapy, since K_{ATP} channels are found in many tissues, including the brain and muscle (8,9), and play a role in membrane polarization and cell functions. Anecdotal case reports support this possibility (2,7,10).

We hypothesized that a successful switch from insulin to SU in patients with neonatal diabetes owing to K_{ATP} channel mutations would improve developmental parameters. We conducted a prospective single-center cohort study of patients successfully switched from insulin to SU therapy. In-depth neurodevelopmental assessments were performed just before the switch and then 12–18 months later.

Table 1—Characteristics of the 18 study patients

Mutations	*n* of patients; patient no.
KCNJ11	
G228A	*n* = 1; 13
E227K	*n* = 1; 14
E292G	*n* = 1; 10
H186D	*n* = 1; 5
I182T	*n* = 1; 9
Q51G	*n* = 1; 8
R201C	*n* = 2; 16, 18
R201H	*n* = 7; 1, 2, 3, 7, 11, 15, 17
V59M	*n* = 1; 12
ABCC8	
R1183W	*n* = 1; 4
R1380H	*n* = 1; 6

Characteristics	Before SU therapy	During SU therapy, month 12 or 18§
Age at SU initiation, years, median (range)	5.3 (0.1–18.5)	
Males, *n* (%)	13 (72)	
HbA_{1c}, %, median (range)	7.75 (5.5–12.8)	6.4 (5.4–10)
Basal C-peptide, ng/mL, median (range)*	0.07 (0.02–0.51)	0.28 (0.12–0.82)**
Stimulated C-peptide, ng/mL, median (range)*	0.1 (0.05–1.44)	0.74 (0.2–1.99)**
Glibenclamide dosage, mg/kg/day, median (range)		0.2 (0–1.43)

*C-peptide measured using a glucagon stimulation test; **$P < 0.01$; §month 12 for basal and stimulated C-peptide and month 18 for HbA_{1c} and glibenclamide dosage.

RESEARCH DESIGN AND METHODS

The appropriate ethics committee (CPP Île-de-France 1) approved the study. SUs are not licensed for use in children in France, and we therefore obtained approval for SU therapy in our patients from both the CPP Île-de-France 1 and the French Healthcare Agency (ANSM). Written informed consent was obtained from the parents or patients before study inclusion.

Study Population

We prospectively included 19 patients seen at the Pediatric Endocrinology and Diabetology Unit of Hôpital Universitaire Necker Enfants Malades Paris between 10 July 2006 and 4 February 2009 who had neonatal diabetes owing to documented mutations in the coding sequence of *KCNJ11* or *ABCC8*. Exclusion criteria were known hypersensitivity to SUs, severe renal failure (creatinine clearance <30 mL/min), severe hepatic failure (prothrombin rate <70%), porphyria, imidazole therapy, pregnancy, or no coverage by the statutory health care insurance system. Of the 19 patients, 18 completed the study and 1 was withdrawn when the parents decided to decline the switch from insulin to SU.

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Table 2—Assessment using NP-MOT at baseline and then 12 months after starting SU therapy in 8 patients younger than 4 years of age at baseline (patient nos. 1–8)

	Abnormal at baseline	Abnormal after 12 months of SU	Median score difference (range)
Tone			
Passive tone	6 (75)	1 (12.5) Improved *n* = 5 Stable *n* = 1 Still normal *n* = 2	−1 (−1 to 0), *P* = 0.06**
Standing tone (score <8)	6 (75)	0 (0%) Improved *n* = 6 Still normal *n* = 2	2 (0−6), *P* = 0.03**
Motricity			
Gross motor skills (delay >2 months)	3 (37.5)	1 (12.5) Improved *n* = 3 Degradation *n* = 1 Still normal *n* = 4	2 (−7 to 3), *P* = 0.19**
Fine motor skills (delay >2 months)	5 (62.5)	2 (25) Improved *n* = 3 Stable *n* = 2 Still normal *n* = 3	1 (−5.5 to 3.5), *P* = 0.07**
Attention			
Attention	3 (37.5)	1 (12.5) Improved *n* = 2 Stable *n* = 1 Still normal *n* = 5	*P* = 0.48*
Hyperactivity	2 (33.3)	0 Improved *n* = 2 Still normal *n* = 6	—

Data are *n* (%) unless otherwise indicated. The value presented in the parentheses in the last column is the range of score differences in values for the patients. The lowest score is −1 and 0 is the highest. *McNemar χ^2 test; **Paired Wilcoxon test on continuous scores.

The switch from insulin to oral SU (glibenclamide) was performed as previously described (5,6). Patients were evaluated 2, 6, 12, and 18 months after inclusion.

French Neuromotor Functions in Children Battery

The French Neuromotor Functions in Children (NP-MOT) battery (11) was performed at baseline and then after 12 months to evaluate development via qualitative (movements) and quantitative (speeds) assessments of muscle tone, gross motor control, laterality, praxis, gnosopraxis (12), digital and manual dexterity, body spatial integration, rhythmic tasks, and an auditory attentional task (12,13). (See Supplementary Data for details.) The NP-MOT battery is a standardized normative instrument with identical subtests for all ages (and expected saturation for patients aged 8 years or older) developed and validated by L.V.-D. For most of the tests, the cutoffs vary with age. Test scores are standardized according to scoring guidelines and expressed as SD of the population mean (failure if <1 SD) or as the percentile (failure if <20th percentile).

Overall test-retest reliability of the NP-MOT has been reported to range from 70 to 98% (11), and correlation coefficients with the Lincoln-Oseretsky motor development scale (similar to the Bruininks-Oseretsky Test of Motor Proficiency [14] for upper-limb coordination, balance, and bilateral coordination subtests) were 0.72 and 0.84 in two studies (15,16).

Developmental, Language, and Sociability Assessment

The same pediatric neurologist conducted a thorough neurological evaluation at baseline and then 6 and 12 months after SU initiation. An electroencephalogram was recorded at baseline in all patients.

Intellectual performance was evaluated at baseline and then after 12 months by the same examiner. All children completed all subtests of a standard measure of intelligence (Brunet-Lézine test, Wechsler Preschool and Primary Scale of Intelligence–Revised [17], Wechsler Intelligence Scale for Children–Fourth Edition [18], or Wechsler Adult Intelligence Scale–Third Edition). Other specific standardized tests consisted of visual-perceptual-motor tests assessing visual construction skills (reproduction of a block design [19]), visual-spatial structuring (manual copy followed by visual-spatial memory of a complex geometric figure [20]), and the Development Test of Visual-Motor Integration (21), which involves manually copying 24 geometric drawings of progressively increasing complexity. Visual-spatial attention was assessed using a bell-crossing test (22) similar to that developed by Gauthier, Dehaut, and Joanette. Mental executive function was evaluated using the Porteus Maze Test (23) and the Tower of London test (24). In addition, the patients performed visual perception (visual gnosis) tasks (recognizing tangled lines and naming animals seen in outline from the rear) (25) and a language screening battery (22). Hyperactivity was defined using the DSM criteria. Children's behavior was observed by the same examiner at inclusion and 12 months after the switch. The examiner recorded the symptoms characterizing the disorder: inattentiveness, impulsivity, and overactivity. Parents were administered an interview covering a broad range of child behaviors. As a part of this interview, parents were asked about the presence/absence of hyperactivity symptoms.

Electrophysiological Assessment of Visual Function

Each patient underwent an electroretinogram and visual evoked potential recordings, as recommended by the International Society for Clinical Electrophysiology of Vision (26,27), at baseline and then 6 months later. Flash visual evoked potentials were recorded in younger patients (monocular, patient no. 10, or binocular if patching an eye was not possible, patient nos. 1, 6, 18, 15, 7, 12, and 14) and pattern reversal visual evoked potentials in older patients (100% contrast; reversal at 1.0 Hz; 60′, 30′, or 15′ squares, patient nos. 4, 9, 11, 17, 3, 5, and 16). No recordings were performed in patient nos. 2 and 13.

Electrophysiological Muscle and Nerve Testing

Electrophysiological testing was performed at baseline and then after 6 and 12 months in children older than 6 years of age and carrying a KCNJ11 mutation (as SUR1 expressed by ABCC8 is

Table 3—Assessment using NP-MOT at baseline and then 12 months after starting SU therapy in 10 patients aged 4–18 years (patient nos. 9–18)

	Abnormal at baseline	Abnormal after 12 months of SU	Change from baseline to 12 months	Median difference (range) (M0/M12) for score*
Tone				
Tone (score <7)	9 (90)	9 (90)	Improved *n* = 7 Stable *n* = 2 Still normal *n* = 1	1 (0–4), *P* = 0.016
Limb and standing tone	7 (70)	5 (50)	Improved *n* = 3 Stable *n* = 4 Still normal *n* = 3	−1 (−1 to 0), *P* = 0.25
Laterality				
Laterality score (score <4)	9 (90)	2 (20)	Improved *n* = 8 Stable *n* = 1 Still normal *n* = 1	1.5 (0–3), *P* = 0.008
Gesture conception: intending a motor action				
Executive function (PA <10% of CA)	4 (0)	5 (40)	Improved *n* = 0 Stable *n* = 4 Still normal *n* = 5 Degraded *n* = 1	0.02 (−29 to 35), *P* = 0.57
Gesture conception: sensory integration				
Auditory attention (score <4)	7 (70)	6 (60)	Improved *n* = 4 Stable *n* = 3 Still normal *n* = 3	0 (0–2), *P* = 0.13
Visual attention (score <34)	9 (90)	7 (70)	Improved *n* = 8 Stable *n* = 1 Still normal *n* = 1	4 (0–20), *P* = 0.008
Digital perception (score <3)	5 (50)	4 (40)	Improved *n* = 1 Stable *n* = 4 Still normal *n* = 4	0 (0–1), *P* = 1
Gesture conception and realization: building the motor program and executing the movement				
Dynamic motor skills (score <7)	9 (90)	7 (70)	Improved *n* = 3 Stable *n* = 6 Still normal *n* = 1	0 (−3 to 5), *P* = 0.50
Static motor skills (score <3)	4 (40)	4 (40)	Improved *n* = 1 Stable *n* = 3 Still normal *n* = 6	0 (0–1), *P* = 1
General praxia (score <4)	9 (90)	7 (70)	Improved *n* = 4 Stable *n* = 5 Still normal *n* = 1	0 (0–3), *P* = 0.13
Two-handed praxia (score <5)	8 (80)	8 (80)	Improved *n* = 4 Stable *n* = 4 Still normal *n* = 2	0 (0–2), *P* = 0.13
Gesture imitation (score <5)	8 (80)	7 (70)	Improved *n* = 5 Stable *n* = 3 Still normal *n* = 2	0.5 (0–2), *P* = 0.06
Body spatial integration (score <4)	8 (80)	8 (80)	Improved *n* = 5 Stable *n* = 3 Still normal *n* = 2	0.5 (0–2), *P* = 0.06
Visual-motor integration (score <13 or 17–19)	10 (100)	10 (100)	Improved *n* = 1 Stable *n* = 9	0 (0–4), *P* = 0.50
Visual-spatial construction	9 (90)	9 (90)	Improved *n* = 3 Stable *n* = 6 Still normal *n* = 1	15 (0–50), *P* = 0.06

Data are *n* (%) unless otherwise indicated. CA, chronological age; M0, baseline (just before starting SU therapy); M12, 12 months after starting SU therapy; PA, performance age. *Paired Wilcoxon test on continuous scores.

not expressed in the muscle). A standardized protocol ensuring reproducible and painless electrophysiological testing of skeletal muscle excitability was used (28). Briefly, compound muscle action potentials were recorded from the right and left abductor digiti minimi muscles after supramaximal electrical stimulation of the ulnar nerves at the wrists. Recordings were repeated before and after voluntary contraction of the recorded muscle. If the response changed after exercise, care was taken to check that the electrode positions were unchanged and that nerve stimulation remained supramaximal.

Table 4—Developmental assessment in 7 patients younger than 2.5 years of age (patient nos. 1, 2, 3, 4, 6, 7, and 8)

	Median (range) PA-CA difference at M0	Median (range) PA-CA difference at M12	Median (range) change M0 vs. M12*	*N* improved pts	*P***	*N* of affected at M0/M12
Global development	−2.5 (−3.5 to 1)	−2.5 (−5 to 3)	−0.5 (−4 to 3.5)	0	0.66	5/5
Posture	−2 (−3.5 to 1)	−1 (−5 to 3.5)	0.8 (−5 to 3.5)	1	0.84	4/3
Coordination	−2.5 (−4.5 to 1)	−2.5 (−8 to 2.5)	−0.5 (−4 to 3.5)	1	0.81	4/4
Language	−2.5 (−5.5 to 1)	−4.5 (−5 to 3.5)	−1.3 (−5 to 4.5)	0	0.38	4/5
Sociability	−2 (−5.5 to 0.5)	−2.5 (−5 to 1.5)	−1 (−2.5 to 2.5)	0	0.47	4/4

Patients were tested using the Brunet-Lézine test at baseline and then 12 months after starting SU therapy. CA, chronological age; M0, baseline (just before starting SU therapy); M12, 12 months after starting SU therapy; PA, performance age; pts, patients. *One patient (patient 2) was not evaluated at the 12-month time point. **Paired Wilcoxon test on continuous scores.

Two provocative tests were performed. The first was a repeated short exercise test at room temperature on the left hand (three maximal, isometric, 10-s abductor digiti minimi contractions separated by 50-s rest periods during which compound muscle action potentials were recorded every 5–10 s). Then, a long exercise test was performed at room temperature on the right hand (maximal, isometric, 5-min abductor digiti minimi contraction followed by compound muscle action potential recording every 5 min for 40 min). Compound muscle action potential amplitude, total duration, and total area were expressed as percentages of pre-exercise values.

Needle electrode recordings were obtained from five muscles (deltoid, extensor digitorum communis, first interosseus dorsalis, vastus medialis, and tibialis anterior) to look for myotonic discharges or evidence of myopathy. Finally, motor conduction of the ulnar and peroneal nerves and sensory conduction of the right and left superficial peroneal nerves were measured. Amplitude, latency, and conduction velocity of the electrophysiological signals were compared with normal values for the laboratory.

Cerebral MRI

MRI was performed at baseline. High-resolution images were acquired using a 1.5-T Signa System machine (GE Healthcare, Milwaukee, WI) with a three-dimensional T1-weighted fast spoiled gradient recalled imaging sequence (repetition time [TR]/echo time [TE]/inversion time/NEX: 10.5/2.2/600/1, 10°, matrix 256 · 192; 124 axial slices, 1.2-mm thickness, 124 contiguous slices, 22 cm field of view), an axial fast spin echo T2-weighted sequence (TR/TE: 6,000/120, 4-mm slices, 0.5 mm gap, 22 cm field of view), coronal fluid-attenuated inversion recovery (FLAIR) sequences (TR/TE/TI: 10,000/150/2,250, 4-mm slices, 1-mm gap, 24 cm field of view), and ^{1}H-MRS.

Pharmacological Assessment

Plasma glibenclamide concentrations were determined after standard liquid-liquid extraction by liquid chromatography–ion-trap tandem mass spectrometry as previously described (29).

Statistical Analysis

Data were described as median (range or interquartile range where indicated) for quantitative variables and as number (percentage) for qualitative variables. Comparisons of data at different time points were performed with the paired Wilcoxon or McNemar test. The nonlinear mixed-effect modeling program NONMEM (version VII, release 1) was used to compute the area under the curve of glibenclamide concentrations over 24 h.

RESULTS

Study Population

We studied 18 patients aged 5 months to 18 years; eight were younger than 4 years old. Metabolic control improved after the switch to glibenclamide therapy, and no patients experienced hypoglycemia. One patient had a remission allowing glibenclamide discontinuation after the 12-month evaluation (Table 1).

Median glibenclamide dosage was 0.37 mg/kg/day (range 0–1.4) at month 18. Median plasma glibenclamide concentration was 50 μg/L (interquartile range 21.5–118), and median area under the time curve over 24 h was 1,335 μg · L/h (511–2,122).

Neurological Evaluation

Neurological impairments were found in a single patient (patient no. 17) and consisted of a global pyramidal syndrome with spasticity and mild walking disability, mild mental retardation, and seizures (DEND). The baseline electroencephalogram was

Table 5—Developmental assessment in 10 patients older than 2.5 years of age

	Median (range) at M0	Median (range) at M12	Median (range) change M0 vs. M12	*N* of improved pts	*P****	*N* of affected at M0/M12
Total IQ (*n* = 10)	60 (40–92)	61.5 (40–94)	0.5 (−13 to 6)	0	0.95	6/6
Verbal IQ (*n* = 6)	80 (45–106)	83 (47–85)*	−1 (−21 to 4)*	0	1	2/2
Performance IQ (*n* = 6)	66 (47–85)	79 (45–100)*	1 (−7 to 15)*	0	0.63	3/2
Verbal Comprehension Index (*n* = 8)	61 (45–96)*	75.5 (45–99)	0 (−7 to 15)*	1	0.94	4/3
Perceptual Reasoning Index (*n* = 8)	60 (45–90)*	57.5 (47–99)	1 (0 to 21)*	0	0.13	4/3
Working Memory Index (*n* = 8)	71 (50–98)*	83.5 (50–100)	2 (0 to 18)*	1	0.13	3/3
Processing Speed Index (*n* = 9)	75 (50–114)**	71 (50–108)	0 (−6 to 11)**	1	0.88	3/4

Tests used: Wechsler Preschool and Primary Scale of Intelligence–Revised for children and Wechsler Intelligence Scale for Children–Fourth Edition for patients younger than 16 years and 11 months old at inclusion (patient nos. 10, 11, 12, 13, 15, 16, 17, and 18) and Wechsler Adult Intelligence Scale–Third Edition for children older than 17 years old (patient nos. 9 and 14). M0, baseline (just before starting SU therapy); M12, 12 months after starting SU therapy; pts, patients. *One patient was not evaluated. **Two patients were not evaluated. ***Paired Wilcoxon test on continuous scores.

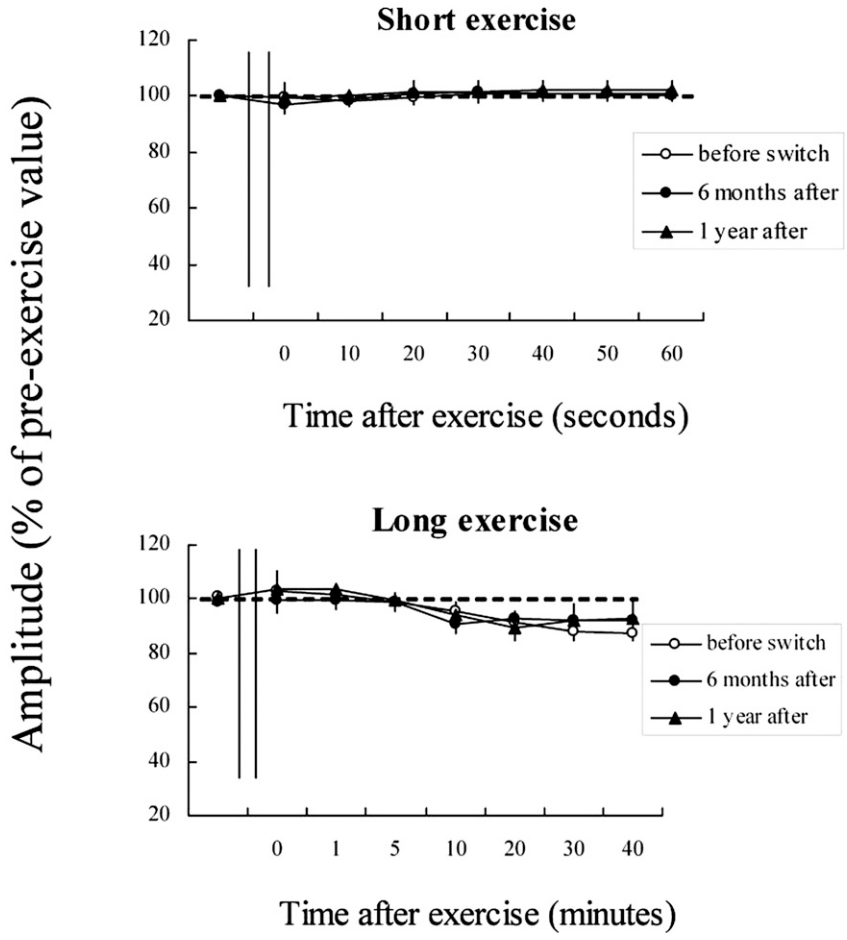

Figure 1—Electrophysiological test results in 10 of 18 patients. Change in compound muscle action potential during short and long exercise tests at baseline and then after 6 and 12 months of oral SU therapy.

normal in 15 patients and abnormal in three (patient nos. 10 and 12, frontal spikes, and no. 17, temporal spikes).

Motor Skills

As previously reported, NP-MOT showed developmental coordination disorder, attention deficit, or both in 17 of the 18 patients. Impairments in the planning or programming of movements were combined with hypotonia in 15 patients. Tables 2 and 3 report the impairments at baseline and the improvements after 12 months of SU therapy. Individual results are reported in Supplementary Tables 1 and 2.

These abnormalities improved markedly after 12 months of SU therapy. Thus, in young children, tone was closer to the normal for chronological age and attention disorders had resolved, with normalization of gross motor skills in all children but one and of fine motor skills in three children. In children older than 4 years of age, tone, visual attention, and laterality improved. These changes benefited gesture conception and realization by ameliorating sensory integration and central gesture planning. Thus, body spatial integration, gesture imitation, and visual-spatial integration were improved. Motor skills were the area with the greatest improvements during SU therapy.

Language

Language disorders or delay were found in six patients at inclusion. They were not improved after 12 months of therapy (Tables 4 and 5).

Sociability and Hyperactivity

Social skills were altered at inclusion in four children younger than 4 years of age. Two children presented with hyperactivity. Sociability was not significantly improved after 12 months of SU, whereas hyperactivity had resolved (Tables 1, 4, and 5).

Development and Intelligence Scores

Development was moderately delayed in five children younger than 2.5 years of age. In older children, intelligence scores were altered. Total IQ score was decreased in four patients. None of these items improved significantly with SU therapy in either age-group (Tables 4 and 5).

Electrophysiological Assessment of Visual Function

Ophthalmoscopy, ocular anatomy, and electroretinography were normal in all patients. Visual evoked potentials were delayed in all but one of the eight youngest patients. Pattern reversal potentials were normal in all but one patient. After 5 months of SU therapy, follow-up examinations in five of eight patients showed normalization of visual evoked potentials in two patients.

Electrophysiological Muscle and Nerve Testing

The 10 patients who underwent electrophysiological testing had normal motor and sensory nerve conduction studies at baseline. The short and long exercise tests induced minor and nonsignificant changes in compound muscle action potential amplitude and area, suggesting absence of membrane excitability impairments (Fig. 1).

Cerebral MRI

MRI was performed in 17 patients (one family refused MRI) and was abnormal in 12 (71%). Nonspecific findings included cerebellar venous angioma (n = 1), posterior periventricular white matter abnormalities (n = 4), and Virshow-Robin space dilation (n = 2). Eight patients had multiple punctate white matter hyperintensities on T2 and FLAIR sequences (Fig. 2*B*), and two had hyperintensities in the nucleus raphe pontis (Fig. 2). ^{1}H-MRS was consistently normal.

CONCLUSIONS

We conducted a systematic prospective evaluation of potential effects of SU therapy in patients with neonatal diabetes owing to K_{ATP} channel mutations. In keeping with our previous work (3), severe neurological deficiencies were uncommon, whereas developmental coordination disorders, language impairments, and attention deficiencies were often detected when appropriate tests were used. Electrophysiological testing showed no

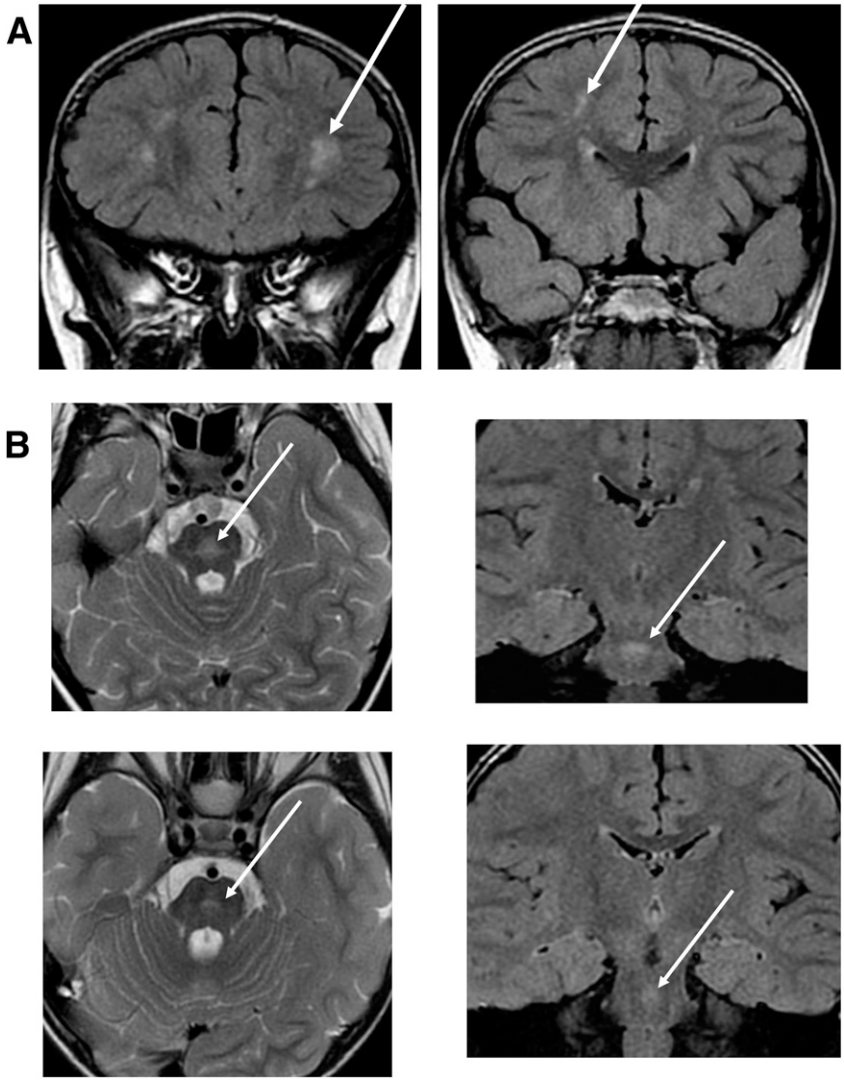

Figure 2—*A*: MRI showing multiple punctate white matter hyperintensities on coronal FLAIR sequences (arrows). *B*: MRI showing brain stem hyperintensities (arrows) in the nucleus raphe pontis in two different children (top images, 4-year-old patient; bottom images, 2.5-year-old patient) on axial T2 and coronal FLAIR sequences.

evidence of the membrane excitability alterations reported in muscle channelopathies, suggesting a neurological origin to the hypotonia and motor impairments. The detection by cerebral MRI of white matter abnormalities in most patients supports a central neurological origin to the motor and developmental impairments. The electrophysiological assessment of visual function also argued for a central origin, as it showed alterations in central sensory integration. Motor abnormalities were noticeably improved after 12 months of SU therapy. In the younger patients, hypotonia and attention deficits were greatly improved or corrected, contributing to ameliorations in motor skills. In patients older than 4 years, tone, laterality, and visual functions showed the greatest improvements, and these contributed to measurable improvements in gesture conception and realization. Neither intelligence scores nor language impairments improved within the study period, whereas hyperactivity was corrected in the affected patients. SU plasma concentrations and area under the curve values were within the therapeutic range for adults (29). Our findings support an effect of SU therapy on the central nervous system in patients with permanent or transient neonatal diabetes owing to *KCNJ11* or *ABCC8* mutations. This effect seems to target specific brain regions, as the greatest improvements were for cerebellar functions (tone, gesture imitation, and body spatial integration) and thalamic functions (tone, laterality, gesture imitation, and visual-spatial construction) involved in various steps of gesture conception and realization such as sensory integration and motor planning.

Several anecdotal case reports are consistent with our findings. A 23-month-old boy with a *KCNJ11* mutation and marked developmental delay experienced substantial improvements in motor function and attention with no change in intelligence scores (30). SU therapy started at 12 years of age in a boy who had a *KCNJ11* mutation induced marked improvements in mental and motor function, with an increase in the Mental Developmental Index from 29 to 39 months within 6 months (7). Attention and gross and fine motor skills improved. MRI showed white matter abnormalities similar to those in our population. In a 6-year-old girl with a *KCNJ11* mutation, improvements in muscle tone, motor function, attention, and hyperactivity were apparent 7 months after switching to SU therapy (10). A study of 19 children with *KCNJ11* mutations focused on visuomotor performance, which correlated negatively with age at SU initiation; however, the patients were tested on a single occasion: after SU initiation (31). In our study, SU therapy in the younger patients was associated with a direct neuronal effect, improving visual conduction and thereby sensory integration and visual attention. This effect probably participated in the motor gains by improving the integration of visual sensory signals.

The neurological and developmental abnormalities seen in patients with neonatal diabetes owing to *KCNJ11* or *ABCC8* mutations are the result of the genetic abnormality and not of diabetes. Furthermore, they are ascribable to the effects of the mutation in central nervous system cells rather than to muscle excitability impairments. The Kir6.2 and SUR1 subunits are widely expressed in all brain regions in rodents and probably form the K_{ATP} channel pores in most neurons (8,9). K_{ATP} channels are also found in muscle. However, we found no evidence of abnormalities in muscle responses to exercise in patients with mutations in the *KCNJ11* gene that encodes the Kir6.2 subunit. In contrast, exercise-induced decreases in the amplitude and area of compound muscle action potentials have been reported in patients with periodic paralysis due to mutations

in sodium (SCN4A), calcium (CACNA1S), or Kir2.1 potassium (KCNJ2) channel genes (28,32). Thus, the muscle disorders in patients with *KCNJ11* mutations do not seem ascribable to changes in muscle membrane excitability. Furthermore, they are ascribable to the effects of the mutation in central nervous system cells rather than to muscle excitability impairments (33). None of our patients had a history of recurrent severe hypoglycemia. The MRI changes in our patients differ from those reported in children with type 1 diabetes (34,35). These last two facts support the direct effect on the central nervous system rather than an indirect effect due to improved metabolic control.

Limitations of our study include the small sample size, although we included most of the patients in France who had neonatal diabetes owing to potassium-channel subunit mutations and had not yet been switched to SU. A control group would have been ethically unacceptable. The short study period was sufficient to see substantial coordination disorders improvement allowing complex tasks such as handwriting to be better performed. If we found no major changes in language, intelligence, or sociability, these functions might improve with time, as this short study was sufficient to correct hyperactivity signs, or, alternatively, SUs may fail to target the brain regions involved. A major strength of our study is the use of a standardized normative neurodevelopmental test battery validated in normal French children and performed by a single examiner. This battery allowed us to obtain accurate information about SU effects on developmental parameters.

SUs have already been suggested as a neuroprotective drug after strokes (36,37). Our findings strongly suggest that SU therapy improves neurodevelopmental parameters in patients with neonatal diabetes owing to potassium-channel subunit mutations and acts via a central mechanism. The greater improvements in younger patients indicate a need for establishing the diagnosis early to allow prompt initiation of SU therapy. Further follow-up of our patients will provide information about the kinetics of SU effects on neurodevelopmental parameters.

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Author Contributions. J.B., K.B., and A.S. collected data. J.B., C.E., K.B., and M.P. wrote the manuscript. J.B., C.E., M.B., and J.M.-T. analyzed data. K.B., A.S., I.F., and M.P. designed the study. E.F. performed the electromyography and analyzed the results. N.B. performed the MRI and analyzed the results. N.B.-B. performed the neurological examination. M.V. performed the intelligence tests. E.B.-Q., I.I.-M., and M.B. performed the electrophysiological assessment of visual function and analyzed the results. C.G. and Z.D. performed the pharmacological assessment. R.S. reviewed the manuscript. H.C. performed the genetic analysis. L.V.-D. performed the neuropsychomotor tests. M.P. 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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Appendix

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References

1. Iafusco D, Massa O, Pasquino B, et al.; Early Diabetes Study Group of ISPED. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1: 90,000 live births. Acta Diabetol 2012;49:405–408
2. Slingerland AS, Shields BM, Flanagan SE, 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;52:1683–1685
3. Busiah K, Drunat S, Vaivre-Douret L, et al.; French NDM study group. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study [corrected]. Lancet Diabetes Endocrinol 2013;1:199–207
4. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350:1838–1849
5. Babenko AP, Polak M, Cavé H, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med 2006;355:456–466
6. Pearson ER, Flechtner I, Njølstad PR, et al.; Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006;355:467–477
7. Slingerland AS, Hurkx W, Noordam K, et al. Sulphonylurea therapy improves cognition in a patient with the V59M KCNJ11 mutation. Diabet Med 2008;25:277–281
8. Li B, Xi X, Roane DS, Ryan DH, Martin RJ. Distribution of glucokinase, glucose transporter GLUT2, sulfonylurea receptor-1, glucagon-like peptide-1 receptor and neuropeptide Y messenger RNAs in rat brain by quantitative real time RT-PCR. Brain Res Mol Brain Res 2003;113:139–142
9. Thomzig A, Laube G, Prüss H, Veh RW. Pore-forming subunits of K-ATP channels, Kir6.1 and Kir6.2, display prominent differences in regional and cellular distribution in the rat brain. J Comp Neurol 2005;484:313–330
10. Mlynarski W, Tarasov AI, Gach A, et al. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. Nat Clin Pract Neurol 2007;3:640–645
11. Vaivre-Douret L. *Batterie d'évaluation des fonctions neuro-psychomotrices (NP-MOT) de l'enfant*. Paris, France, Editions du Centre de Psychologie Appliquée, 2006 [in French]
12. Vaivre-Douret L. A more robust predictor of ideomotor dyspraxia: study on an alternative scoring method of the Bergès-Lézine's Imitation of Gestures test. Arch Clin Neuropsychol 2002;17:37–48
13. Vaivre-Douret L. *Evaluation of the Distal Motricity Control, Revision and Adaptation Bergés-Lézine's Test*. Paris, France, Editions du Centre de Psychologie Appliquée, 1997 [in French]

14. Bruininks H. *Bruininsks-Oserestky Test of Motor Proficiency*. Circles Pines, MN, American Guidance Service, 1978
15. Vaivre-Douret L. Developmental and cognitive characteristics of "high-level potentialities" (highly gifted) children. Int J Pediatr 2011;2011:420297
16. Vaivre-Douret L, Lalanne C, Ingster-Moati I, et al. Subtypes of developmental coordination disorder: research on their nature and etiology. Dev Neuropsychol 2011;36:614–643
17. Wechsler D. *Wechsler Preschool and Primary Scale of Intelligence*. San Antonio, TX, The Psychological Corporation, 1989
18. Wechsler D. *Manual for the Wechsler Preschool and Primary Scale of Intelligence-Revised*. San Antonio, TX, The Psychological Corporation, 1989
19. Khos C. *Test des Cubes de Khos*. Paris, France, Editions du Centre de Psychologie Appliquée, 1972 [in French]
20. Rey A. *Manuel test de copie d'une figure complexe*. Paris, France, Editions du Centre de Psychologie Appliquée, 1959 [in French]
21. Beery KE. *Revised Administration Scoring and Teaching Manual for the Development Test of Visual-Motor Integration (VMI)*. Toronto, ON, Canada, Modern Curriculum Press, 1982
22. Jaquier-Roux M, Valdois S, Zorman M, et al. *ODEDYS Outil de dépistage des dyslexies*, version 2, Cogni-Sciences, IUFM, Paris, France, 2005 [in French]
23. Porteus SD. *Test des Labyrinthes de Porteus*. Paris, France, Editions du Centre de Psychologie Appliquée, 1952 [in French]
24. Korkman MKU. *Developmental Neuropsychological Assessment Manual*. Paris, France, Editions du Centre de Psychologie Appliquée, 2003
25. Rey A. L'examen psychologique dans le cas d'encéphalopathie traumatique. Arch Psychol 1941;112:286–340 [in French]
26. Odom JV, Bach M, Brigell M, et al. ISCEV standard for clinical visual evoked potentials (2009 update). Doc Ophthalmol 2010;120:111–119
27. Marmor MF, Fulton AB, Holder GE, Miyake Y, Brigell M, Bach M; International Society for Clinical Electrophysiology of Vision. ISCEV standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol 2009;118:69–77
28. Fournier E, Arzel M, Sternberg D, et al. Electromyography guides toward subgroups of mutations in muscle channelopathies. Ann Neurol 2004;56:650–661
29. Hoizey G, Lamiable D, Trenque T, et al. Identification and quantification of 8 sulfonylureas with clinical toxicology interest by liquid chromatography-ion-trap tandem mass spectrometry and library searching. Clin Chem 2005;51:1666–1672
30. 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 2006;49:2559–2563
31. 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 2012;35:2086–2088
32. Bendahhou S, Fournier E, Sternberg D, et al. In vivo and in vitro functional characterization of Andersen's syndrome mutations. J Physiol 2005;565:731–741
33. Clark RH, McTaggart JS, Webster R, et al. Muscle dysfunction caused by a KATP channel mutation in neonatal diabetes is neuronal in origin. Science 2010;329:458–461
34. Barnea-Goraly N, Raman M, Mazaika P, et al.; Diabetes Research in Children Network (DirecNet). Alterations in white matter structure in young children with type 1 diabetes. Diabetes Care 2014;37:332–340
35. Marzelli MJ, Mazaika PK, Barnea-Goraly N, et al.; Diabetes Research in Children Network (DirecNet). Neuroanatomical correlates of dysglycemia in young children with type 1 diabetes. Diabetes 2014;63:343–353
36. Kunte H, Schmidt S, Eliasziw M, et al. Sulfonylureas improve outcome in patients with type 2 diabetes and acute ischemic stroke. Stroke 2007;38:2526–2530
37. Simard JM, Yurovsky V, Tsymbalyuk N, Melnichenko L, Ivanova S, Gerzanich V. Protective effect of delayed treatment with low-dose glibenclamide in three models of ischemic stroke. Stroke 2009;40:604–609