Long-term Metabolic and Socioeducational Outcomes of Transient Neonatal Diabetes: A Longitudinal and Cross-sectional Study

Diabetes Care 2020;43:1191–1199 | https://doi.org/10.2337/dc19-0324

*Fleur Le Bourgeois,[1] Jacques Beltrand,[2,3] Baz Baz,[4] Jean-Baptiste Julla,[5] Jean-Pierre Riveline,[4,5] Albane Simon,[6] Isabelle Flechtner,[2] Malek Ait Djoudi,[7] Anne-Laure Fauret-Amsellem,[8] Yoann Vial,[8,9] Raphael Scharfmann,[3] Julie Sommet,[1] Philippe Boudou,[10] Hélène Cavé,[8,9] Michel Polak,[2,3] Jean-François Gautier,[4,5] Kanetee Busiah,[2,11] and the TNDM Long-Term Follow-Up Study Group**

[1]*Department of Pediatric Critical Care and Intensive Care, Robert Debré Teaching Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France*
[2]*Department of Pediatric Endocrinology, Gynecology, and Diabetology, Necker-Enfants Malades Teaching Hospital, Assistance Publique-Hôpitaux de Paris, IMAGINE Institute Affiliate, Paris, France*
[3]*INSERM Unité Médicale de Recherche UMR 1016, Université de Paris, Sorbonne Paris Cité, Paris, France*
[4]*Department of Diabetes and Endocrinology, Lariboisière Hospital, Assistance Publique-Hôpitaux de Paris and Université de Paris, Paris, France*
[5]*INSERM UMRS 1138, Centre de Recherches des Cordeliers, Université de Paris, Sorbonne Paris Cité, Paris, France*
[6]*Department of Pediatrics, André Mignot Hospital, Le Chesnay, France*
[7]*Centre Universitaire du Diabète et ses Complications, Hôpital Lariboisière, Clinical Investigation Center, INSERM-CIC 9504, Paris, France*
[8]*Department of Genetics, Robert Debré Teaching Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France*
[9]*Université de Paris, Sorbonne Paris Cité, Paris, France*
[10]*Unit of Hormonal Biology, Department of Biochemistry, Saint-Louis University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France*
[11]*Pediatric Endocrinology, Diabetology and Obesity Unit, Lausanne University Hospital, Lausanne University, Lausanne, Switzerland*

Corresponding author: Jean-François Gautier, jean-francois.gautier@aphp.fr

Received 15 February 2019 and accepted 5 March 2020

Clinical trial reg. no. NCT02072551, clinicaltrials.gov

This article contains Supplementary Data online at https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0324/-/DC1.

**A complete list of the members of the TNDM Long-Term Follow-Up Study Group is available in the Supplementary Data online.*

M.P., J.-F.G., and K.B. contributed equally to this work.

OBJECTIVE

Transient neonatal diabetes mellitus (TNDM) occurs during the 1st year of life and remits during childhood. We investigated glucose metabolism and socioeducational outcomes in adults.

RESEARCH DESIGN AND METHODS

We included 27 participants with a history of TNDM currently with ($n = 24$) or without ($n = 3$) relapse of diabetes and 16 non-TNDM relatives known to be carriers of causal genetic defects and currently with ($n = 9$) or without ($n = 7$) diabetes. Insulin sensitivity and secretion were assessed by hyperinsulinemic-euglycemic clamp and arginine-stimulation testing in a subset of 8 TNDM participants and 7 relatives carrying genetic abnormalities, with and without diabetes, compared with 17 unrelated control subjects without diabetes.

RESULTS

In TNDM participants, age at relapse correlated positively with age at puberty ($P = 0.019$). The mean insulin secretion rate and acute insulin response to arginine were significantly lower in TNDM participants and relatives of participants with diabetes than in control subjects (median 4.7 [interquartile range 3.7–5.7] vs. 13.4 [11.8–16.1] pmol/kg/min, $P < 0.0001$; and 84.4 [33.0–178.8] vs. 399.6 [222.9–514.9] μIU/mL, $P = 0.0011$), but were not different between participants without diabetes (12.7 [10.4–14.3] pmol/kg/min and 396.3 [303.3–559.3] μIU/mL, respectively) and control subjects. Socioeducational attainment was lower in TNDM participants than in the general population, regardless of diabetes duration.

CONCLUSIONS

Relapse of diabetes occurred earlier in TNDM participants compared with relatives and was associated with puberty. Both groups had decreased educational attainment, and those with diabetes had lower insulin secretion capacity; however, there was no difference in insulin resistance in adulthood. These forms of diabetes should be included in maturity-onset diabetes of the young testing panels, and relatives of TNDM patients should be screened for underlying defects, as they may be treated with drugs other than insulin.

Neonatal diabetes mellitus (NDM) is defined as mild-to-severe hyperglycemia requiring treatment within the 1st year of life. In the transient form of NDM (TNMD), diabetes resolves in the early years of life but usually relapses later on (1). The two main genetic abnormalities responsible for TNDM are 6q24 abnormalities (2) and activating mutations in genes encoding the ATP-sensitive potassium (K_{ATP}) channel subunits *KCNJ11* (KIR6.2) (3) and *ABCC8* (SUR1) (4). Less commonly, mutations in the preproinsulin (*INS*) gene are involved (5,6).

The metabolic and other phenotypic features of TNDM during the neonatal period have been described. In contrast, few data are available on glucose metabolism during the remission, relapse, and adulthood (7,8). We reported previously that relapse rates did not differ between the 6q24 and K_{ATP} groups (1). No studies have identified factors associated with relapse of diabetes. It has been shown that relatives who were known carriers of TNDM causal genetic defects may present with TNDM, late-onset diabetes, or no history of diabetes (9). Moreover, in addition to diabetes, other features, such as neurological impairments, may be present during childhood in patients with TNDM, including those with 6q24 abnormalities (1).

The underlying mechanism of occurrence of diabetes is still unknown. Our objectives here were to investigate the long-term metabolic outcomes in adults with a history of TNDM or who were known carriers of TNDM causal genetic defects but without a history of TNDM, the risk factors of relapse or occurrence of diabetes in adolescence or adulthood, and the socioeducational attainment of adults with TNDM and of their non-TNDM genetic abnormalities–carrying relatives.

RESEARCH DESIGN AND METHODS

Study Design and Participants

Our cohort of patients with NDM has been described elsewhere (1). Here, we performed cross-sectional and retrospective assessments of long-term outcomes in those NDM cohort patients who had history of TNDM and in their adult relatives who were known carriers of causal genetic defects. We divided the population into four groups that were defined as follows: TNDM participants with and without relapsing diabetes and genetic abnormalities–carrying relatives with and without diabetes at the time of the study (Fig. 1 and Supplementary Fig. 1). None of the genetic abnormalities–carrying relatives had experienced TNDM. TNDM was defined as hyperglycemia requiring treatment before the age of 1 year, followed by a remission of the diabetes in childhood, defined as normal glycemic control without treatment. Diabetes relapse was defined as the development of overt diabetes meeting World Health Organization criteria after remission. We included participants who lived in France and were older than 18 years on 1 June 2016. Participants gave written informed consent before inclusion. The study complied with the Declaration of Helsinki as revised in 2013. The DNA bank and phenotypic database were reported to French health authorities in compliance with current legislation.

Data Collection

We collected data from the cohort database. Missing information was sought by conducting a semistructured questionnaire during a face-to-face or telephone interview with the participant or his or her general practitioner or diabetologist between 1 September 2013 and 1 June 2016. For each participant, we recorded the following data: gestational age, birth weight, and birth length; age at diabetes onset, glycemia, and age at insulin withdrawal; age at diabetes relapse and mode of relapse; Tanner pubertal stage when available (assessed by their pediatrician or their pediatric diabetologist) and age at menarche for girls; metabolic parameters (HbA_{1c}, intravenous [IV] glucose tolerance test); anthropometric data; treatment modality and dose at diabetes onset, diabetes relapse, and last follow-up; treatment adherence; pregnancies; long-term complications; metabolic and neurological outcomes; academic history and final educational attainment; and socioeconomic status. Reference values for educational attainment and socioeconomic status were from two different samples, one composed of 5,496 individuals born and living in France, aged 18–30 years, and included in the 2003 Decennial Health Survey by the French National Institute of Statistics and Economic Studies (10) and the other provided by the French Ministry of Education, composed of 24,000 children who started sixth grade in France in 1989. Birth weight and length percentiles were calculated according to French growth charts (AUDIPOG [Association des Utilisateurs de Dossiers Informatisés en Périnatalogie, Obstétrique et Gynécologie]).

Assessment of Insulin Sensitivity and Secretion

To differentiate between insulin sensitivity and insulin secretion disorders, a two-step protocol was conducted at the Clinical Investigations Unit of the Saint Louis Teaching Hospital (Paris, France). A 75-g oral glucose tolerance test (OGTT) was performed in TNDM participants and genetic abnormalities–carrying relatives without diabetes. In participants with diabetes (TNDM participants and genetic abnormalities–carrying relatives), the treatment was discontinued 48 h before the exploration day, and insulin was infused to maintain a glycemia $<$11 mmol/L during the night before the test. Then, all participants were fasting from 8 P.M.

The first step was a hyperinsulinemic-euglycemic clamp (11). The second consisted in measuring the maximal insulin secretion in response to a graded IV glucose infusion, followed by a bolus of arginine (glucose ramping) (12). The tests are detailed in the Supplementary Data. The control group consisted of 17 healthy subjects with normal glucose tolerance, assessed by an OGTT. Their first and second-degree relatives had no known history of type 2 diabetes. They were not related to our participants and had no history of TNDM. All control subjects had normal findings from a physical examination and routine laboratory tests. Those control subjects were pair-matched to the participants on age ($\pm$10 years), sex, and BMI ($\pm$3 kg/m^2). As a control group, we did not find anyone with diabetes that could be pair-matched to the study participants on age and BMI.

Percentage body fat mass and fat-free mass in the subset of 15 TNDM participants and genetic abnormalities–carrying relatives were measured by DEXA (LUNAR iDXA, ME+ 200027; GE Healthcare, Chicago, IL).

Calculations

The insulin secretion rate (ISR) during glucose ramping was calculated by C-peptide deconvolution (11) and plotted against the corresponding mean glucose

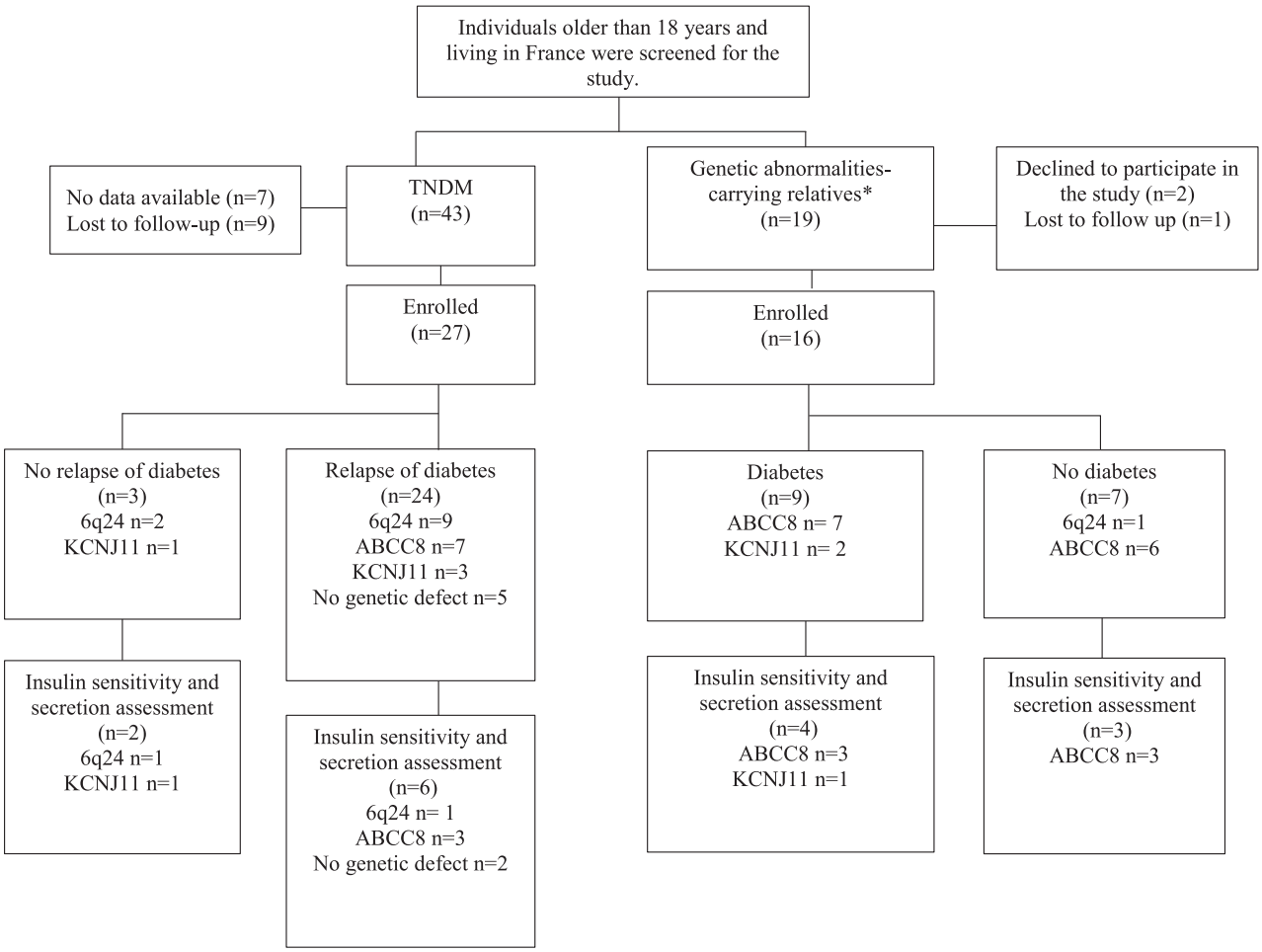

Figure 1—Participant flow diagram. *No genetic abnormalities–carrying relatives had a history of TNDM.

concentration. Mean ISR-40 min was calculated using the ISR values measured every 5 min during the last 40 min of glucose ramping. We also determined the acute insulin response to arginine (AIR_{Arg}) as the mean of the 2- to 5-min plasma insulin levels minus the basal (prearginine) plasma insulin levels (13). Insulin-stimulated glucose disposal rate (M) was calculated from the glucose infusion rate during the last 20 min (at 80, 90, and 100 min) of the glucose clamp after accounting for interindividual differences in glucose space and was expressed in mg/kg of fat-free mass/min (14,15).

Genetic Analyses

We assessed changes in the 6q24 locus and mutations in the K_{ATP}-channel subunit (*ABCC8* and *KCNJ11*) and preproinsulin genes (*INS*) known to be associated with TNDM. DNA was unavailable for seven TNDM participants, all of whom were lost to follow-up. Peripheral blood from TNDM participants and genetic abnormalities–carrying relatives was collected on EDTA, and DNA was extracted using standard procedures. We tested all TNDM participants and genetic abnormalities–carrying relatives for 6q24 abnormalities, as previously described (1). *ABCC8*, *KCNJ11*, and *INS* were screened for mutations using bidirectional sequencing of the whole gene-coding sequence and flanking intron–exon boundaries (1).

Statistical Analysis

Qualitative data are described as number (percentage) and quantitative data as median (interquartile range). We compared the groups with 6q24 abnormalities, K_{ATP} channel subunit mutations, and no identified molecular defects by using the Kruskal-Wallis test for quantitative data and the Fisher exact test for qualitative data. To compare characteristics of TNDM participants who were included in the study and those lost to follow-up and to compare socioeducational attainment in our TNDM participants and in the general population, we applied the Wilcoxon test for quantitative data and the Fisher exact test for qualitative data. The Pearson test was chosen to assess correlations. For comparisons of metabolic results, we used the Kruskal-Wallis test. If the overall comparison was significant, we conducted pairwise comparisons using the Wilcoxon test. For each individual, we calculated mean ISR-40 min as the mean of ISR values measured every 5 min during the last 40 min of glucose ramping. Results from different patients are expressed as median (interquartile range). Values of $P < 0.05$ were considered significant.

RESULTS

Participants and Genetic Findings

Among the potential participants, 27 with TNDM and 16 relatives harboring the same genetic abnormalities were enrolled for the study (Fig. 1). We found no differences in clinical or laboratory data between the 9 TNDM participants lost to follow-up and the 27 included

(Supplementary Table 1). Genetic abnormalities were detected in 22 of 27 TNDM participants (Fig. 1) and in all genetic abnormalities–carrying relatives (Supplementary Table 2).

Diabetes Relapse in TNDM Participants and Associated Factors

Of the 27 TNDM participants, 24 (89%) experienced a diabetes relapse with no subsequent remission at a median age of 13.8 years (Table 1). The oldest age at relapse was 45.5 years (*KCNJ11* mutation p.Gln179Lys). Age at menarche was available for 15 of the 17 females (89%) and genital Tanner stage for 2 of 7 males (38%) whose diabetes relapsed. Age at relapse correlated positively with age at puberty ($R^2 = 0.58$; $P = 0.019$). Median time from menarche to relapse was 0.6 years. BMI at relapse was available for 19 patients and was not associated with age at relapse ($R^2 = 0.018$, $P = 0.94$). Details on the mode of diagnosis of the diabetes relapse were available for 18 TNDM participants, of whom 8 had polyuria-polydipsia. No one experienced ketoacidosis during the relapse. The most common treatment at relapse was subcutaneous insulin alone ($n = 15$ [63%]) (Table 1). There was no difference in characteristics of TNDM participants according to genetic etiology (Supplementary Table 3).

Of the three TNDM participants who did not have diabetes at the time of the study, two, aged 18 and 20 years, had 6q24 abnormalities. The remaining TNDM participant, aged 20 years, had a *KCNJ11* mutation (p.Gln179Lys, patient 8 in Supplementary Tables 2 and 4) and had experienced a transient diabetes relapses of 1.5 years' duration at 17.3 years of age that was first treated with insulin (0.06 IU/kg/day) and then gliclazide. She stopped all treatment at 18.5 years. She is currently on a balanced diet and is regularly physically active. Her HbA_{1c} is 6.1% (43 mmol/mol).

Among participants with current diabetes, when the TNDM group was compared with the genetic abnormalities–carrying group, we found that TNDM participants were younger at diabetes relapse than were the genetic abnormalities–carrying relatives at diabetes occurrence (median 13.8 [interquartile range (IQR) 12.0–16.0] years vs. 22 [16.0–26.0] years, $P = 0.002$). The mode of diagnosis and the treatment did not differ (Table1).

Insulin Sensitivity and Secretion in Adulthood

There were 15 participants (8 women and 7 men) who volunteered to undergo an investigation of insulin sensitivity and secretion as follows: 8 TNDM participants (53.3%) (6 with current diabetes and 2 without relapse of diabetes) and 7 genetic abnormalities–carrying relatives (46.7%) (4 with diabetes and 3 without diabetes) (Table 1 and Supplementary Table 4). Their median age was 25 (IQR 20.5–38) years, and the median BMI was 20.8 (IQR 19.2–23.3) kg/m^2.

During glucose ramping (Table 2), mean ISR was significantly lower in participants with diabetes compared with those without diabetes (median 4.7 [IQR 3.7–5.7] vs. 12.7 [10.4–14.3] pmol/kg/min, $P = 0.0047$) and with the control subjects without diabetes (4.7 [3.7–5.7] vs. 13.4 [11.8–16.1] pmol/kg/min, $P < 0.0001$).

During the arginine stimulation test (Table 2), AIR_{Arg} was significantly lower in the individuals with diabetes than in the control subjects without diabetes (84.4 [33.0–178.8] vs. 399.6 [222.9–514.9] μIU/mL, $P = 0.0011$) but was not different between TNDM participants and genetic abnormalities–carrying relatives with versus without diabetes (84.4 [33.0–178.8] vs. 396.3 [303.3–559.3] μIU/mL, $P = 0.076$). Among participants with current diabetes, when comparing the TNDM group to the genetic abnormalities–carrying group, we found no difference in mean ISR (4.14 [3.08–4.71] vs. 5.13 [3.67–7.85] pmol/kg/min, $P = 0.3523$), AIR_{Arg} (40.88 [21.34–99.80] vs. 57.5 [46.21–168.60] μIU/mL, $P = 0.47619$), and M value (12.54 [9.99–15.03] vs. 11.94 [10.27–13.54] mg/kg/min, $P = 1$) (Supplementary Table 4). Insulin sensitivity, as measured by the M value, was not different across groups.

Metabolic Outcome in TNDM Participants With Sustained Relapses and in Their Relatives

TNDM participants ($n = 24$) were younger than genetic abnormalities–carrying relatives ($n = 16$) at the last follow-up (Table 1). Diabetes duration was shorter for TNDM participants than for genetic abnormalities–carrying relatives (median 11.1 [IQR 5.5–14.9] vs. 19.0 [6.0–27.0] years, $P = 0.013$). TNDM participants who relapsed had a lower BMI than their genetic abnormalities–carrying relatives with diabetes (20.8 [17.9–22.2] vs. 27.1 [22.5–28.5] kg/m^2, $P = 0.009$), but their HbA_{1c} did not differ (7.0% [6.5–8.1] vs. 7.3% [6.7–8.7], $P = 0.40$). Regarding their treatment, TNDM participants were more often on insulin therapy alone, at a median dose of 0.5 IU/kg/day, than their genetic abnormalities–carrying relatives (11 of 23 vs. 0 of 9, $P = 0.03$). The most commonly used oral antidiabetes drug (OAD) was sulfonylureas in both groups (TNDM participants: $n = 8$ of 12, relatives: $n = 6$ of 7), alone or in dual therapy with another OAD or insulin.

Data on long-term complications were available for 14 TNDM participants (58%) with sustained relapses. Their median diabetes duration since relapse was 13.7 (6.1–19.5) years, and median HbA_{1c} was 6.6% (6.3–8.1) (49 [45–65] mmol/mol). Among them, three individuals had retinopathy (stage 1 or 2), including one who also had chronic kidney disease (glomerular filtration rate 30 mL/min/1.73 m^2) diagnosed during a pregnancy 15 years after the relapse. No one had neuropathy based on clinical examination.

Among genetic abnormalities–carrying relatives, 13 had *ABCC8* mutations, 2 had *KCNJ11* mutations, and 1 had 6q24 abnormalities (Supplementary Table 2). Nine relatives (56%) had diabetes, which was diagnosed at a median age of 22 (16–26) years (Fig. 1). The mode of diagnosis of the diabetes was polyuria-polydipsia ($n = 3$), hyperglycemia diagnosed by routine follow-up testing ($n = 4$), and hyperglycemia diagnosed during pregnancies ($n = 2$). No one experienced ketoacidosis. At the last follow-up, median diabetes duration was 19 (6–27) years and median HbA_{1c} was 7.3% (6.7–8.7) (53 [50–72] mmol/mol); the treatment was an OAD agent alone ($n = 6$ [54%]) or long-acting subcutaneous insulin combined with an OAD ($n = 3$ [27%]). The OAD was a sulfonylurea in seven relatives with diabetes (gliclazide, $n = 1$; glibenclamide, $n = 4$; and glimepiride, $n = 2$). Data on long-term complications were available for six relatives, who had a median diabetes duration of 21 (10.7–31.6) years and a median HbA_{1c} of 7% (6.7–7.0) (57 [50–53] mmol/mol). Two had retinopathy (stage 1). No one had neuropathy or nephropathy.

Socioeducational Attainment in Adulthood in TNDM Participants and in Their Genetic Abnormalities–Carrying Relatives

Of 24 TNDM participants, 8 (33%) had repeated their first grade because of

Table 1—Characteristics at diabetes relapse or diagnosis and at last follow up for 27 TNDM participants (with diabetes relapse or not) and 16 genetic abnormalities–carrying relatives (with diabetes or not)

	TNDM participants		Genetic abnormalities–carrying relatives		*P* value TNDM participants with and without relapse of diabetes	*P* value TNDM participants vs. genetic abnormalities–carrying relatives, all with current diabetes
	With relapse ($n = 24$)	With no relapse* ($n = 3$)	With diabetes ($n = 9$)	Without diabetes ($n = 7$)		
Genetic abnormalities						
6q24 abnormalities, *n*	9	2	0	1		
K_{ATP} channel mutations, (*KCNJ11* and *ABCC8*), *n*	10	1	9	6		
No identified molecular defect, *n*	5	0	0	0		
Clinical and biological characteristics of TNDM participants at time of relapse and relatives at time of diabetes diagnosis						
Age at relapse/diagnosis, years, *n*	24/24		9/9			
Median (IQR)	13.8 (12.0–16.0)	NA	22 (16.0–26.0)	NA	NA	0.002
Anthropometry						
BMI at relapse/diagnosis, *n*	19/24	NA	1/10	NA	NA	NA
kg/m^2, median (IQR)	18.5 (17.6–21.4)					
Z-score, median (IQR)	0.2 (−1.1 to 0.7)	NA	−2	NA	NA	NA
BMI *Z*-score $> +2$, *n*	1	NA	0	NA	NA	NA
Age of menarche/male gonadal stage 2, years, *n*	17/24	NA	1/10	NA	NA	NA
Median (IQR)	13.0 (12.0–15.0)	NA	15	NA	NA	NA
Diagnosis, *n*	18/24	NA	9/9	NA		
Polyuria-polydipsia, *n*	8	NA	3	NA	NA	1
Hyperglycemia diagnosed during						
Infection†, *n* (%)	4 (17)	NA	0	NA	NA	0.55
Follow-up, *n* (%)	6 (25)	NA	4	NA	NA	0.40
Pregnancy, *n*	0	NA	2	NA	NA	0.07
Ketoacidosis, *n*	0	NA	0	NA	NA	NA
HbA_{1c}, *n*	15/24	NA	0/9	NA		
%, median (IQR)	8.0 (6.5–10.9)	NA	NA	NA	NA	NA
mmol/mol, median (IQR)	64 (48–96)	NA	NA	NA	NA	NA
Treatment, *n*	24/24	NA	8/9	NA		
Insulin alone, *n*	15/24	NA	5/8	NA	NA	1
Dose, IU/kg/day, median (IQR)	0.7 (0.4–0.8)	NA	NA	NA		
OAD alone, *n*	8/24	NA	3/8	NA	NA	1
Sulfonylurea	6	NA	2	NA		
Other	2	NA	1	NA		
Combined insulin and OAD, *n*	1/24	NA	0/8	NA	NA	1
Sulfonylurea	1	NA	NA	NA		
Insulin dose, IU/kg/day	0.75	NA	NA	NA		
Clinical and biological characteristics of TNDM participants at last follow-up						
Age, years, *n*	24/24	3/3	9/9	5/7		
Median (IQR)	23.3 (20.1–29.3)	19.4 (18.6–19.8)‡	43.0 (38.4–50.0)	40.0 (37.5–50.2)	0.08	<0.001
Diabetes duration, years, *n*	24/24	NA	9/9	NA	NA	
Median (IQR)	11.1 (5.5–14.9)	NA	19.0 (6.0–27.0)	NA		0.013
BMI, kg/m^2, *n*	22/24	3/3	7/9	2/7		
Median (IQR)	20.8 (17.9–22.2)	19.4 (19.2–19.9)‡	27.1 (22.5–28.5)	21.2 (19.0–23.3)‡	0.56	0.009
HbA_{1c}, *n*	23/24	3/3	8/9	3/7		
%, median (IQR)	7.0 (6.5–8.1)	5.3 (5.1–6.1)‡	7.3 (6.7–8.7)	5.8 (5.7–6.2)‡	0.01	0.40
mmol/mol, median, (IQR)	53 (48–65)	34 (32–43)	53 (50–72)	40 (39–44)		
Treatment, *n*	23/24	NA	7/9	NA		
Insulin alone, *n*	11	NA	0	NA	NA	0.03
Dose, IU/kg/day, median (IQR)	0.50 (0.45–0.65)	NA	NA	NA		
OAD alone, *n*	10	NA	4	NA	NA	0.68
One OAD	7	NA	2	NA		
Two OADs	3	NA	2	NA		
Sulfonylurea	6	NA	3	NA		

Continued on p. 1196

Table 1—Continued

	TNDM participants		Genetic abnormalities–carrying relatives		*P* value TNDM participants with and without relapse of diabetes	*P* value TNDM participants vs. genetic abnormalities–carrying relatives, all with current diabetes
	With relapse ($n = 24$)	With no relapse* ($n = 3$)	With diabetes ($n = 9$)	Without diabetes ($n = 7$)		
Combined insulin and OAD, *n*	2	NA	3	NA	NA	0.12
Dose, IU/kg/day, median (IQR)	0.48§	NA	0.15 (0.09–0.20)‡	NA		
Sulfonylurea	2	NA	3	NA		

NA, not applicable. *Of the three patients who did not relapse, mean age at the study of 19 years, two (a man and a woman) had 6q24 abnormalities. The remaining patient, a woman aged 20 years, had a *KCNJ11* mutation (p.Glu179Lys) and had experienced a transient diabetes relapses of 1.5 years' duration at 17.3 years of age that was first treated with insulin (0.06 IU/kg/day) and then gliclazide. She stopped all treatment at 18.5 years, and she is currently on a balanced diet and is regularly physically active. †Infections at diagnosis: two patients with vulvar mycosis, one with appendicitis, and one with sore throat. ‡Because of a small *n* we choose to use minimum and maximum. §The daily insulin dose was known for one patient.

difficulty learning to read (Table 3 and Supplementary Table 5). This proportion was significantly higher than in the general population (7%, $P < 0.0001$). Six individuals (25%) reported difficulty with spatial orientation in childhood.

The proportion of TNDM participants who completed their secondary education was significantly lower than in the general population (29% vs. 12%; $P = 0.02$). There were more TNDM participants outside the labor market than in the general population (22% vs. 5%; $P = 0.004$).

The educational attainment and socioeconomic status were not statistically different between TNDM participants and their relatives ($n = 13$). Diabetic condition did not change educational attainment and socioeconomic status (Supplementary Table 5).

CONCLUSIONS

Our study provides the first data on the long-term metabolic and socioeducational outcomes of individuals with TNDM history and their relatives carrying the same genetic abnormalities. The genetic defect does not predict the diabetes relapse in TNDM participants or the occurrence of diabetes in relatives. Insulin response to glucose or to arginine stimuli is not associated with the underlying genetic defects in adulthood. TNDM participants had learning difficulties and a lower educational attainment than the general population. They were significantly more often outside the labor market but did not differ for other socioeconomic status.

Diabetes relapse was common in our population of adults with a history of TNDM, in line with our findings in a pediatric cohort (1). Furthermore, we provide the largest cohort with long-term follow-up duration. A 1995 review described the outcomes of 32 patients with TNDM, of whom only 5 were adults. Median follow-up after diabetes relapse was 3 years. However, long-term remissions persisting into the fifth decade have been reported in our cohort and in another study (2).

Relapse rate is not associated with genetic subtype (1). In adults, the same mutation is detected in individuals with or without diabetes. This led us to hypothesize that relapse is independent of the underlying genetic abnormalities. The pathophysiology of relapsing diabetes in individuals with TNDM history may involve insufficient insulin secretion demonstrated here and by others (16) and revealed during the insulin resistance state physiologically associated with puberty. In TNDM individuals, our group previously demonstrated that during the first 2 years of diabetes remission, there was no evidence of fasting insulin resistance or β-cell dysfunction, although β-cell function may be at the lower extremity of the normal range (7). At the time of diabetes relapse, the absence of ketoacidosis and low insulin requirements are consistent with residual endogenous insulin secretion. On the other hand, low birth weight is associated with subsequent insulin resistance (17), and 68% of individuals with TNDM had intrauterine growth restriction (1). Here, the correlation between age at diabetes relapse and age at puberty may be ascribable to higher insulin resistance just before and during puberty than in younger children (18–20). In adulthood, this insulin resistance decreases in TNDM participants and their genetic abnormalities–carrying relatives, as shown by their similar M values to those of control subjects without diabetes.

However, the questions of the absence of postpubertal remission in TNDM and the postpubertal occurrence of diabetes in non-TNDM genetic abnormalities–carrying relatives remain. It is a known phenomenon in pregnancy, as 50% of women with gestational diabetes mellitus develop type 2 diabetes within 5 years after pregnancy (21,22). The mechanism is poorly understood but might involve interindividual variability of insulin sensitivity and β-cell mass. In addition, the impact of glucotoxicity on β-cell mass cannot be excluded (23,24). Conceivably, individuals with current diabetes (TNDM participants and genetic abnormalities–carrying relatives) may have an abnormally small β-cell mass (25,26). Precise measurement of the β-cell mass remains challenging in humans. The combined IV glucose and arginine stimulus has been proposed as an indicator of the maximal insulin secretion capacity reflecting β-cell mass (27). Thus, our AIR_{Arg} results support a decrease in maximal insulin secretion capacity to both glucose and arginine stimuli that reflect low β-cell mass. Surprisingly, we found a trend and not a statistical difference in AIR_{Arg} between participants with and without diabetes (TNDM participants and genetic abnormalities–carrying relatives). This might be due to the small sample size and to the wide distribution of AIR_{Arg} values of these patients.

Our failure to identify strong factors associated with diabetes relapse or occurrence may be ascribable to the small sample size. Nevertheless, a mild

Table 2—Evaluation of insulin sensitivity and secretion in 15 individuals (8 patients with TNDM and 7 genetic abnormalities–carrying relatives) and 17 control subjects (no history of diabetes and TNDM) by euglycemic-hyperinsulinemic clamp and glucose ramping

	Current diabetes and genetic abnormalities, TNDM (n = 6), relatives (n = 4)	No current diabetes despite genetic abnormalities, TNDM (n = 2), relatives (n = 3)§	Control subjects	P value (overall comparison)	P value (diabetes and genetic abnormalities vs. control subjects)	P value (diabetes and genetic abnormalities vs. no diabetes despite genetic abnormalities)
	n = 10	n = 5	n = 17			
Mean ISR-40 min* (pmol/kg/min)	4.7 (3.7–5.7)	12.7 (10.4–14.3)	13.4 (11.8–16.1)	0.0002	<0.0001	0.0047
AIR_{Arg}† (μIU/mL)	84.4 (33.0–178.8)	396.3 (303.3–559.3)	399.6 (222.9–514.9)	0.0069	0.0011	0.0750
M value‡ (mg/kg/min)	12.5 (9.6–15.1)	14.3 (14.1–16.3)	12.3 (11.8–14.0)	0.281	—	—

Data are median (IQR). *The ISR during glucose ramping was calculated by C-peptide deconvolution and plotted against the corresponding mean glucose concentration. The mean ISR value is the mean of ISR values measured every 5 min during last 40 min of glucose ramping. †The acute insulin response to arginine was determined as the mean of plasma levels after 2–5 min minus the basal (prearginine) plasma concentration. ‡The M value measures the insulin-stimulated glucose disposal rate during a hyperinsulinemic-euglycemic clamp, in mg/kg of fat-free mass/min. §The comparison of participants with no diabetes despite mutations to control subjects with no diabetes showed no significant differences.

deficiency in insulin secretion might be a predictive factor for diabetes onset. Among individuals with a genetic alteration associated with TNDM, those who do not have diabetes tend to have a higher insulin secretion than individuals with diabetes.

We and others previously reported that neurological and neuropsychological disorders, including developmental coordination disorders, were associated with NDM and were more common with K_{ATP}-channel gene mutations than with 6q24 abnormalities (1,28–30).

In the current study, regardless of the underlying genetic abnormalities or the duration of diabetes, TNDM was associated with learning difficulties at school. The reason may be the small sample size. However, another possibility is that some cognitive processes may be impaired in

Table 3—Socioeducational attainment in patients with TNDM and the general population in France

	Patients with TNDM (n = 27)	General population (n = 24,000*)	P value
Diabetes at last follow-up	24 (89)	NA	
Data available, n	22	24,000	
Repeated a class	16 (67)	15,984 (67)	1
Repeated first grade	8 (33)	1,752 (7)	<0.0001
Education tailored to a disability	3 (13)	NC	—
Difficulties with learning to read	8 (33)	NA	—
Difficulties with spatial orientation	6 (25)	NA	—
Developmental delay, epilepsy, and neonatal diabetes			
Severe	0	NA	—
Intermediate	2 (8)	NA	—
Educational attainment, n	24	5,496†	
Primary education	2 (8)	506 (9)	1
Intermediate education	6 (25)	1,511 (28)	1
Lower secondary education	7 (29)	649 (12)	0.02
Higher secondary/tertiary education	9 (36)	2,830 (51)	0.4
Socioeconomic status, n	23	5,496	
Student	5 (22)	1,544 (28)	0.64
Low-grade professional	8 (35)	2,429 (44)	0.41
Intermediate/high-grade professional	5 (22)	1,270 (23)	1
Outside the labor market	5 (22)‡	253 (5)	0.004

Data are n (%) unless otherwise indicated. NA, not applicable; NC, not collected. Socioeconomic status was classified as follows: student; occupation requiring basic skills; occupation requiring a high or intermediate level of education; or unemployed, not economically active, and outside the labor market. *This sample included the 24,000 French children born on the 5th day of any month who started sixth grade in France in 1989. †This sample was composed of 5,496 individuals born and living in France, aged 18–30 years, and included in the 2003 Decennial Health Survey by the French National Institute of Statistics and Economic Studies (INSEE). The INSEE classification of socioeconomic status was used. Participants were classified based on the highest level of education attained: primary school; intermediate level (did not graduate from high school); lower secondary education (equivalent to skilled professionals); graduation from high school or further education. ‡We included housewives in this group.

individuals with TNDM. These data support the use of sulfonylurea treatment in TNDM individuals with *KCNJ11* or *ABCC8* mutations as soon as the slightest impairment in glucose control develops, because this treatment has been shown to improve neurological function (29–32). Moreover, as insulin secretion seems partially impaired at relapse, sulfonylurea may also be useful in individuals with 6q24 abnormalities (33,34).

Our study has several limitations. The participants were scattered throughout the country, and their follow-up was not standardized. Furthermore, knowledge about TNDM has improved in recent years, and data for parameters now known to be relevant, such as glycemic balance during remission, were not collected for the older participants. The high risk of relapse was recognized only recently, and some individuals may therefore not have been closely monitored for relapsing diabetes.

Finally, the difference in therapeutic indications based on genotype is a recent finding. To improve data collection, we contacted each participant and the parents when possible, the pediatricians who had provided care to the patient, and the current general practitioner or diabetologist. If needed, participants were interviewed at home on several occasions to develop a climate of confidence, thereby maximizing the proportion of individuals who consented to the study and ensuring that they understood all the questionnaire items. Because the insulin sensitivity and secretion evaluation was funded by a French institutional grant (ClinicalTrials.gov reg. no. NCT02072551), we were able to include only individuals living in France.

The small number of participants is due to the low incidence of TNDM. The small number of TNDM participants without diabetes reflects the very high relapse rate. Some of the nonsignificant results may be ascribable to insufficient sample size. Moreover, we were unable to establish a control group of individuals with diabetes matched on age and BMI. This is probably because TNDM participants and their relatives carrying the same genetic abnormalities have a different phenotype from that seen in typical type 2 diabetes, particularly a low BMI. Patients with diabetes who are young and lean should be tested with maturity-onset diabetes of the young (MODY) testing panels to have personalized medicine for their diabetes.

Our data on the natural history of TNDM and time of diabetes relapse have implications for clinical practice. The high relapse rate and absence of identified predictors of relapse suggest a need for an HbA_{1c} assay at least every 2 years throughout childhood and for an HbA_{1c} assay and OGTT every year throughout adolescence. During childhood, close attention should be directed to education and neurodevelopmental milestones in patients with and without diabetes.

Finally, the data reported here should prove useful for designing prospective studies of patients and relatives aimed at assessing glucose metabolism throughout childhood or adulthood, identifying predictors of diabetes relapse, collecting long-term complications, and evaluating neuropsychological and educational interventions. The question of how to detect this form of diabetes among adults with diabetes should be further investigated.

Acknowledgments. The authors thank the nursing staff headed by Myriam Faivre and the secretarial staff at the Necker-Enfants Malades Teaching Hospital. The authors are indebted to the families for their contribution. The authors thank Anne Wojtusciszyn (Endocrinology, Diabetology and Metabolism Unit, Lausanne University Hospital, Lausanne University, Lausanne, Switzerland) for revision of the manuscript. The authors dedicate this work to Dr. Jean-Jacques Robert (in memoriam).

Funding. Support was received from Association Française du Diabète (R.S., M.P.). This work was funded by the Agence Nationale de la Recherche-Maladies Rares (ANR-MRAR) Research Program grant #ANR-07-MRAR-000 (M.P.), the Transnational European Research Grant on Rare Diseases #ERANET-09-RARE-005 (M.P.), the Société Francophone du Diabète (M.P.), and Aide aux Jeunes Diabétiques (M.P.).This study was also supported by an institutional grant from Assistance Publique-Hôpitaux de Paris (PHRC AOR011147; Principal Investigator J.-F.G.) and ASSERADT (Association pour l'Etude et la Recherche de l'Amélioration du Traitement du Diabète [a non-profit patient association]). K.B. received a Convention Industrielle de Formation par la Recherche grant from and was supported by HRA-Pharma, the French Ministry of Education and Research, and the Société Française de Pédiatrie. The English was revised by Antoinette Wolfe, who was funded through the grant obtained for this work.

The study sponsors had no role in the design and conduct of the study, data collection, data analysis, data interpretation, or preparation, review, or approval of the manuscript and decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. F.L.B., J.B., M.P., and K.B. wrote the manuscript. F.L.B., J.-B.J., J.-P.R., J.-F.G., and K.B. collected and analyzed the data. F.L.B., J.S., and K.B. performed the statistical analysis. J.B., M.P., and K.B. performed and/or were responsible for patient follow-up. B.B. was responsible for the in-depth metabolic assessments. A.S. and I.F. cared for the patients and participated in part of the data collection. M.A.D. collected data for the in-depth metabolic assessments. A.-L.F.-A. and H.C. performed and/or were responsible for the genetic tests and their interpretation. Y.V. performed the genetic tests. R.S. performed critical revisions and provided final approval of the study. P.B. was responsible for the hormonal assays of the in-depth metabolic study and performed critical revisions. M.P., J.-F.G., and K.B. conceived and designed the study. All authors critically revised and approved the final manuscript. J.-F.G. and K.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. 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 [published correction appears in Lancet Diabetes Endocrinol 2013;1:e14]. Lancet Diabetes Endocrinol 2013;1:199–207
2. Temple IK, Shield JPH. 6q24 transient neonatal diabetes. Rev Endocr Metab Disord 2010;11:199–204
3. 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
4. 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
5. Garin I, Edghill EL, Akerman I, et al.; Neonatal Diabetes International Group. Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. Proc Natl Acad Sci U S A 2010;107:3105–3110
6. Bonnefond A, Lomberk G, Buttar N, et al. Disruption of a novel Kruppel-like transcription factor p300-regulated pathway for insulin biosynthesis revealed by studies of the c.-331 INS mutation found in neonatal diabetes mellitus. J Biol Chem 2011;286:28414–28424
7. Shield JPH, Temple IK, Sabin M, et al. An assessment of pancreatic endocrine function and insulin sensitivity in patients with transient neonatal diabetes in remission. Arch Dis Child Fetal Neonatal Ed 2004;89:F341–F343
8. von Mühlendahl KE, Herkenhoff H. Long-term course of neonatal diabetes. N Engl J Med 1995;333:704–708
9. Alkorta-Aranburu G, Carmody D, Cheng YW, et al. Phenotypic heterogeneity in monogenic diabetes: the clinical and diagnostic utility of a gene panel-based next-generation sequencing approach. Mol Genet Metab 2014;113:315–320
10. Caille J-P. Le redoublement à l'école élémentaire et dans l'enseignement secondaire: évolution des

redoublements et parcours scolaires des redoublants au cours des années 1990–2000. Éducation et Formation 2004;69:79–88
11. Sobngwi E, Boudou P, Mauvais-Jarvis F, et al. Effect of a diabetic environment in utero on predisposition to type 2 diabetes. Lancet 2003; 361:1861–1865
12. Gautier J-F, Fetita LS, Riveline J-P, et al. Sex difference in the effect of fetal exposure to maternal diabetes on insulin secretion. J Endocr Soc 2018;2:391–397
13. Larsson H, Ahrén B. Glucose-dependent arginine stimulation test for characterization of islet function: studies on reproducibility and priming effect of arginine. Diabetologia 1998;41:772–777
14. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237:E214–E223
15. Simon M-C, Möller-Horigome A, Strassburger K, et al.; German Diabetes Study Group. Correlates of insulin-stimulated glucose disposal in recent-onset type 1 and type 2 diabetes. J Clin Endocrinol Metab 2019;104:2295–2304
16. Valerio G, Franzese A, Salerno M, et al. Beta-cell dysfunction in classic transient neonatal diabetes is characterized by impaired insulin response to glucose but normal response to glucagon. Diabetes Care 2004;27:2405–2408
17. Nobili V, Alisi A, Panera N, Agostoni C. Low birth weight and catch-up-growth associated with metabolic syndrome: a ten year systematic review. Pediatr Endocrinol Rev 2008;6:241–247
18. Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV. Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. J Clin Endocrinol Metab 1991;72:277–282
19. Jeffery AN, Metcalf BS, Hosking J, Streeter AJ, Voss LD, Wilkin TJ. Age before stage: insulin resistance rises before the onset of puberty: a 9-year longitudinal study (EarlyBird 26). Diabetes Care 2012;35:536–541
20. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res 2006; 60:759–763
21. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373:1773–1779
22. Löbner K, Knopff A, Baumgarten A, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. Diabetes 2006;55:792–797
23. Robertson RP. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. J Biol Chem 2004;279: 42351–42354
24. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care 1990;13:610–630
25. Busiah K, Verkarre V, Cavé H, Scharfmann R, Polak M. Human pancreas endocrine cell populations and activating ABCC8 mutations. Horm Res Paediatr 2014;82:59–64
26. Sanyoura M, Jacobsen L, Carmody D, et al. Pancreatic histopathology of human monogenic diabetes due to causal variants in KCNJ11, HNF1A, GATA6, and LMNA. J Clin Endocrinol Metab 2018; 103:35–45
27. Teuscher AU, Kendall DM, Smets YF, Leone JP, Sutherland DE, Robertson RP. Successful islet autotransplantation in humans: functional insulin secretory reserve as an estimate of surviving islet cell mass. Diabetes 1998;47:324–330
28. Gloyn AL, Diatloff-Zito C, Edghill EL, et al. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. Eur J Hum Genet 2006;14:824–830
29. Shimomura K, Hörster F, de Wet H, et al. A novel mutation causing DEND syndrome: a treatable channelopathy of pancreas and brain. Neurology 2007;69:1342–1349
30. Beltrand J, Elie C, Busiah K, et al.; GlidKir Study Group. Sulfonylurea therapy benefits neurological and psychomotor functions in patients with neonatal diabetes owing to potassium channel mutations. Diabetes Care 2015;38: 2033–2041
31. Koster JC, Cadario F, Peruzzi C, Colombo C, Nichols CG, Barbetti F. The G53D mutation in Kir6.2 (KCNJ11) is associated with neonatal diabetes and motor dysfunction in adulthood that is improved with sulfonylurea therapy. J Clin Endocrinol Metab 2008;93:1054–1061
32. 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
33. Carmody D, Beca FA, Bell CD, et al. Role of noninsulin therapies alone or in combination in chromosome 6q24-related transient neonatal diabetes: sulfonylurea improves but does not always normalize insulin secretion. Diabetes Care 2015;38:e86–e87
34. Garcin L, Kariyawasam D, Busiah K, et al. Successful off-label sulfonylurea treatment of neonatal diabetes mellitus due to chromosome 6 abnormalities. Pediatr Diabetes 2018;19:663–669