Permanent Diabetes Without Serological Evidence of Autoimmunity After Transient Neonatal Diabetes

MICHAEL E. GOTTSCHALK, MD, PHD
DESMOND A. SCHATZ, MD
MICHAEL CLARE-SALZLER, MD
DANIEL L. KAUFMAN, PHD
GRACE S.P. TING, BA
MITCHELL E. GEFFNER, MD

OBJECTIVE — To describe a probable association between TNDM and subsequent permanent IDDM.

RESEARCH DESIGN AND METHODS — A longitudinal follow-up of a single case from birth to 12 yr of age was conducted analyzing sequential OGTTs, ICAs, AIAs, anti-GAD antibodies, and other organ-specific and nonspecific antibodies.

RESULTS — A small-for-gestational-age infant developed hyperglycemia at 20 h of age and required insulin therapy for the 1st 14 wk of life (TNDM). Transient hyperglycemia and ketonuria were noted again at age 2 yr 10 mo during an intercurrent illness, but OGTT was normal; and ICA, AIA, anti-GAD_{65} and anti-GAD_{67} antibodies, antithyroid microsomal, anti–gastric parietal cell, antiadrenal, antisteroidal, and antinuclear antibodies were negative 3 wk later. At age 9 yr, hyperglycemia returned and persisted in the setting of hypoinsulinemia; ICA, AIA, anti-GAD_{65} and anti-GAD_{67} antibodies, and other organ-specific and nonspecific antibodies were again negative. Insulin therapy was initiated and has been maintained over 3 yr of follow-up.

CONCLUSIONS — Our case is the fifth reported with permanent diabetes occurring after resolution of TNDM. The etiology of permanent diabetes in this setting is unknown but, unlike classical IDDM, appears unrelated to autoimmunity in our patient. The true frequency of this association remains unknown.

FROM THE UNIVERSITY OF CALIFORNIA MEDICAL CENTER, DEPARTMENT OF PEDIATRICS, LOS ANGELES, CALIFORNIA; AND THE COLLEGE OF MEDICINE, UNIVERSITY OF FLORIDA, GAINESVILLE, FLORIDA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO MITCHELL E. GEFFNER, MD, UCLA MEDICAL CENTER, DEPARTMENT OF PEDIATRICS, MDCC 22-315, LOS ANGELES, CA 90024.

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TNDM, TRANSIENT NEONATAL DIABETES MELLITUS; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; OGTT, ORAL GLUCOSE TOLERANCE TEST; ICA, ISLET CELL ANTIBODY; AIA, ANTI-INSULIN ANTIBODY; GAD, GLUTAMIC ACID DECARBOXYLASE; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; ATMA, ANTITHYROID MICROSOMAL ANTIBODY; AGPCA, ANTI–GASTRIC PARIETAL CELL ANTIBODY; AAA, ANTI-ADRENAL ANTIBODY; ASA, ANTI-STEROIDAL ANTIBODY; ANA, ANTI-NUCLEAR ANTIBODY.

TNDM is a rare clinical entity with <60 reports published since the first patient was described by Ramsey in 1926 (1). Affected infants are usually small for gestational age and present shortly after birth with hyperglycemia, glycosuria, and dehydration. Less frequently, ketosis, metabolic acidosis, and fever also occur. Insulin therapy is required for a variable period of time, and complete and spontaneous resolution of hyperglycemia is thought to occur by 18 mo of age. Four patients with permanent diabetes mellitus occurring in later childhood or early adulthood after remission of TNDM have been reported. IDDM developed in 3 of these patients at 15, 18, and 20 yr of age (2–5), and one patient developed NIDDM at 12 yr of age (4). Herein, we describe development of permanent diabetes unassociated with serological evidence of autoimmunity in a child who had TNDM.

Case

JM was a full-term female infant born to an 18-yr-old gravida 1 mother by normal spontaneous vaginal delivery in 1979. The mother received prenatal care and had no symptoms of hypoglycemia. Birth weight was 1650 g (−2.66 SD), length 44.5 cm (−1.84 SD), and head circumference 29.5 cm (−3.99 SD). She had a wasted appearance, with a marked decrease in subcutaneous fat. Shortly after birth, her serum glucose concentration was 4.1 mM. At 20 h of age, the serum glucose concentration rose to 27.6 mM. Several other serum glucose levels were >27.8 mM. Na^+ was 132 mM, K^+ 3.6 mM, chloride 106 mM, and CO_2 content 12.6 mM. Ketonuria was absent. An infusion of 0.1 U · kg^{-1} · h^{-1} insulin i.v. was begun, and subsequently the patient received twice-daily subcutaneous NPH insulin. She was discharged from the hospital at 2 mo of age weighing 3560 g (−1.82 SD), consuming 150 kcal · kg^{-1} · day^{-1}, and requiring 1.1–1.4 U NPH insulin every 12 h. By 14 wk of age, hyperglycemia had resolved, and

Table 1—*OGTT*

	TIME (MIN)	GLUCOSE (MM)*	INSULIN (PM)†
AGE			
2 YR 10 MO	0	4.5	71.8
	30	7.4	301
	60	7.6	373
	120	5.9	237
	180	3.2	502
9 YR	0	13.8	35.9
	30	18.4	122
	60	24.8	101
	90	26.3	57.4
	120	25.6	86.1

*To convert to mg/dL, multiply by 18.
†To convert to μU/mL, multiply by 0.1394.

insulin therapy had been gradually discontinued.

Thereafter, she was followed as an outpatient 2–3 times/yr, maintaining normal growth, development, and HbA_1 levels without signs or symptoms of hyperglycemia. Her mother also was tested periodically for glycosuria, which was never present. At age 2 yr 10 mo, glycosuria and 4+ ketonuria were noted at the time of an upper respiratory infection with otitis media and fever. Random blood glucose levels were 9.4–11.5 mM over the next several days. Because dehydration and acidosis were not present, insulin therapy was not instituted. The hyperglycemia and ketonuria resolved within 72 h. Three wk later, an OGTT was performed. Glucose tolerance was normal, as were simultaneous serum insulin levels (Table 1). HbA_1 was 8.0% (normal range = 5.2–8.8%). The patient's family moved to Mexico, and for the next 6 yr, she remained healthy, without recurrence of glycosuria.

At 9 yr of age, she returned for evaluation of asymptomatic nonketotic hyperglycemia. Her height and weight were both at the 50th percentile, and she had a normal physical examination. Over the next 3 wk, daily urine testing was positive only once for glucose. However, the magnitude and frequency of glycosuria increased dramatically, although she remained asymptomatic. A second OGTT was performed, which confirmed the diagnosis of diabetes; relative hypoinsulinemia was present (Table 1); GHb was 13.6% (normal range 4–7%). ICA, AIA, anti-GAD_{65} and anti-GAD_{67}, ATMA, AGPCA, AAA, ASA, and ANA were not detectable. In addition, these antibodies were all negative in a serum sample taken at age 2 yr 10 mo and stored at −20°C. Her HLA type was A24, Bw48, Cw8, DR4. To control hyperglycemia, the patient was started on split mixed-insulin therapy; she is now 12 yr 6 mo old and requires 0.9–1.3 $U \cdot kg^{-1}day^{-1}$ of insulin. The mother's GHb level at 30 yr of age was 5.9% (normal range 4.2–6.8%). The maternal grandfather developed NIDDM at 55 yr of age; otherwise, no family history of diabetes or autoimmune endocrinopathies exists.

RESEARCH DESIGN AND METHODS

— ICAs were assessed by indirect immunofluorescence on blood group O cryocut pancreatic sections, and AIA were measured by modification of the radioimmune binding assay of Palmer et al. (6). We developed a rapid assay for antibodies to both forms of GAD (GAD_{65} and GAD_{67}) (7). *E. coli* expressing human GAD_{65} and GAD_{67} cDNAs were grown in minimal medium and induced with isopropyl ß-D-thiogalactopyranoside in the presence of a mixture of ^{35}S-labeled amino acids. The bacteria were harvested, sonicated in GAD buffer, and centrifuged to remove debris. Sera were preabsorbed with extracts of unlabeled nonrecombinant host bacteria and then added to a mixture of ^{35}S-labeled extracts of GAD_{65}- and GAD_{67}-producing bacteria. Immunoabsorbed polypeptides were isolated with protein-A sepharose and analyzed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and autoradiography. GAD, previously known as the M_r = 64,000 autoantigen, has been shown to be an important autoantigen in IDDM (6–8) and the stiff-man syndrome (9). Standard methodologies for ATMA, AGPCA, AAA, ASA, and ANA were used.

CONCLUSIONS

— Our patient had the classical features of TNDM, i.e., intrauterine growth retardation, onset of hyperglycemia shortly after birth, and a several-month postnatal exogenous insulin requirement. In 1969, Gentz and Cornblath (10) reviewed the published reports of 30 patients with TNDM and presented 2 additional patients. In all subjects, diabetes resolved spontaneously in early infancy and did not recur later in life. Since then, four brief reports of permanent diabetes developing during adolescence to early adulthood after TNDM (Table 2) have been published (2–5). All the subjects were small for gestational age at birth and had hyperglycemia beginning between birth and 2 wk of age. Their initial hyperglycemia resolved between 5 and 32 wk of age with permanent diabetes noted between 9 and 20 yr of age.

Several years before developing permanent diabetes, during a concurrent infectious illness, our patient had transient hyperglycemia and ketonuria without acidosis. We have reported previously that transient hyperglycemia or glycosuria during acute illnesses is not uncommon in children, but only infrequently progresses to IDDM (11). Although none of these children with transient hyperglycemia (without TNDM) who subsequently had a normal OGTT developed diabetes (11), those who ultimately developed IDDM had impaired glucose tolerance by OGTT or intravenous glucose tolerance testing shortly after recovery from their episode of transient hyperglycemia (11,12). When overt diabetes ensued in children with transient hyperglycemia, it was within a relatively short time, <18 mo, after the episode of high blood glucose had resolved. In contrast, our patient had normal glucose tolerance 3 wk after an episode of transient hyperglycemia and

Table 2—*Patients with TNDM who later developed permanent diabetes*

Reference no.	Birth weight (kg)	Age of remission of TNDM (wk)	Age of onset of permanent diabetes (yr)	Autoantibodies	HLA type
Campbell et al. (3)	2.13	8	18	ICA^-	A2, A9, B12
Coffey and Killelea (2)	1.74	17	15	ND	ND
Briggs (4)	1.5	32	12	ND	A2, B7, B20
Croxson and Burden (5)	1.6	5	20	ND	ND
Gottschalk et al. (unpublished observations)	1.65	14	9	ICA^-, AIA^-, anti-GAD_{65}^-, anti-GAD_{67}^-, $ATMA^-$, $AGPCA^-$, AAA^-, ASA^-, ANA^-	A24, Bw48, Cw8, DR4

ND, Not done.

developed permanent diabetes many years later. Those patients with transient hyperglycemia (without TNDM) who later developed diabetes typically are ICA^+ (11,12), whereas our patient was persistently ICA^-, AIA^-, anti-GAD^-_{65}, and anti-GAD^-_{67} and lacked other autoimmune-related antibodies, including ATMA, AGPCA, AAA, ASA, and ANA, which can be found in children with IDDM (13). That our patient's permanent diabetes (without ketonuria) could represent a form of maturity-onset diabetes of the young is not likely because of the limited family history of diabetes (14), including her mother's recent normal GHb level.

The etiology of permanent IDDM developing after TNDM appears to be different than that of classical IDDM. Over 80% of patients with IDDM are ICA^+ at the time of diagnosis (15), 70–90% have anti-GAD_{64} antibodies (16), and 20–69% have AIA (17,18). When measured together in the same patients, 82% of children are ICA^+ and/or anti-GAD^+_{64} (19), and 82% are ICA^+ and/or AIA^+ (18). Therefore, in a patient with newly diagnosed IDDM, the probability of lacking all three immunological markers, as was the case of our patient, would be extremely low. Except for lack of ICA in one other patient (3), the immunological status of the patients with TNDM and subsequent IDDM is unknown. Our patient was presumably homozygous for DR4. Although one DR4 allele occurs in 64–80% of people with IDDM (20), DR4 is also present in 40% of the nondiabetic population (20), in which the incidence of IDDM is only 0.3%. Therefore, the presence of DR4 is not useful as a genetic predictor of developing IDDM.

The etiology of TNDM is unknown, and therefore, the reason for subsequent permanent IDDM years later can only be speculative. The most commonly accepted explanation for TNDM is delayed functional maturation of the pancreatic β-cell (21). Affected infants are neither insulinopenic (22) nor insulin resistant (23), although they are glucose unresponsive. Their insulin secretory response is very similar to that of fetal β-cells, demonstrating a differential response to various insulin secretagogues. Affected infants do not secrete insulin in response to glucose or tolbutamide but do respond to caffeine (21). The fetal β-cell likewise, is unresponsive to glucose stimulation, although it readily releases insulin in response to glucagon and theophylline, both of which raise intracellular concentrations of cAMP (24,25). Glucose and tolbutamide stimulate insulin release by altering the β-cell membrane potential through regulating ATP-sensitive K^+ channels (26). GLUT2, the predominant facilitative glucose transporter of the β-cell, is thought to be the putative glucose sensor of pancreatic β-cell regulating insulin release (27,28). Decreased expression of GLUT2 has been demonstrated in animal models of both IDDM and NIDDM (28). Altered expression of GLUT2 could be responsible for the apparent delayed functional maturation of fetal β-cells and β-cells in infants with TNDM. Complete maturation of the insulin response to glucose in preterm infants may not occur until 6 mo of age (29), similar to the length of duration of TNDM. Longitudinal studies on the glucose tolerance of older children and adults who had TNDM would be useful to clarify whether insulin secretion is completely normal or whether subtle defects persist.

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