

LONG-TERM COURSE OF NEONATAL DIABETES

KARL ERNST VON MÜHLEND AHL, M.D., AND HEINER HERKENHOFF, M.D.

Abstract *Background.* Neonatal diabetes mellitus — defined here as hyperglycemia occurring within the first month of life that lasts for at least two weeks and requires insulin therapy — is a very rare form of the disease. Little is known about it, particularly with respect to its long-term course.

Methods. We studied two brothers who had neonatal diabetes and obtained follow-up information on 34 patients described in the literature as well as information on 21 additional patients. Forty-seven of the patients had neonatal diabetes, as defined above, and in 10 others the onset was between the first and third month of life.

Results. Twenty-six of the 57 infants had permanent diabetes, 18 had transient diabetes, and 13 had transient diabetes that recurred when they were 7 to 20 years old.

Neonatal diabetes was associated with the Wolcott-Rallison syndrome in six infants, hyperuricemia due to phosphoribosyl-ATP pyrophosphatase hyperactivity in two, and celiac disease in two. Forty-one of 45 neonates in whom the duration of gestation and birth weight were known were small for their gestational ages. There were two pairs of affected twins and four other families with two or more infants with neonatal diabetes, but only three parents had diabetes. The incidence of neonatal diabetes mellitus in Germany has been estimated to be 1 in 500,000 neonates.

Conclusions. Neonatal diabetes differs from insulin-dependent diabetes in that its course is highly variable. Some patients have permanent diabetes, but others have transient or lasting remissions. (*N Engl J Med* 1995;333:704-8.)

NEONATAL diabetes mellitus is a very rare condition. For this study it is defined as hyperglycemia that requires insulin treatment, occurs during the first month of life, and lasts more than two weeks. Reviewing the literature, we found 123 publications on this subject. Complete remission after various periods of insulin dependency has been described, as have relapses after many years of remission, but about half the patients remained permanently diabetic. In six patients from three families, diabetes with a somewhat later onset (on the 28th to 77th day of life) was associated with multiple epiphyseal dysplasias, renal impairment, and a poor long-term prognosis (the Wolcott-Rallison syndrome).¹⁻³ We found no reports of the association of neonatal diabetes mellitus with other developmental or dysmorphic syndromes.

We recently examined two brothers born in 1986 and 1988 who have hyperuricemia due to phosphoribosyl-ATP pyrophosphatase hyperactivity, a very rare X-linked disease,⁴ and who became diabetic within the first day of life. This encounter led us to collect and analyze in detail the information available about neonatal diabetes. This report describes these two patients and what is known about the long-term course of neonatal diabetes mellitus.

METHODS

We evaluated 123 publications concerning neonatal diabetes; in 64, from 17 countries, we found sufficient information to allow us to contact the authors for follow-up data on individual patients. Considering that many of the publications were old — 47 were published before 1975 — the response (35 answers) was good, and yielded follow-up data on 29 patients. Seven correspondents indicated that they had treated other infants with neonatal diabetes mellitus, and data on six additional infants are included in this survey.

We also sent a questionnaire about neonatal diabetes to the heads of all 230 pediatric departments and clinics in the former West Germany. About 60 percent responded. They had seen 13 infants with neonatal diabetes who were born between 1977 and 1991 and provided data on all of them.

This review is based on the case histories of 57 infants identified

through these investigations. For 7, all data were from previous publications; for 29, additional follow-up data were provided by the authors; and for 21 (including our 2 patients), all the data are new.

Forty-seven of the infants met the definition of neonatal diabetes given above. Another 10, in whom the diabetes began between the first and third months of life, were also included: 5 with the Wolcott-Rallison syndrome, 3 with transient diabetes and later recurrence (included because of the extreme rarity of this course, which indicates that it is clearly distinct from insulin-dependent diabetes of very early onset), and 2 patients (Patients 34 and 35) with permanent diabetes who were described in earlier publications and have now been followed for 36 and 32 years, respectively.

CASE REPORTS

We examined two brothers with hyperuricemia due to phosphoribosyl-ATP pyrophosphatase hyperactivity who became diabetic in the first day of life. The first of the two brothers (Patient 50) was born in 1986. His mother had had abortions of female fetuses in the 16th and 19th weeks of gestation. There are no other children in the family. The pregnancy, which was complicated by preeclampsia, was terminated by cesarean section because of placental insufficiency in the 37th week of gestation. The boy weighed 1390 g and was 39 cm long; the circumference of his head was 29 cm. When he was 1, 5, and 12 hours old, his blood glucose concentrations were 40, 80, and 120 mg per deciliter (2.2, 4.4, and 6.7 mmol per liter), respectively. When he was 24 hours old, his blood glucose concentration was 503 mg per deciliter (27.9 mmol per liter). He was not acidotic and had no clinical manifestations of hyperglycemia. Insulin therapy was begun on the second day of life. The dose ranged from 0.5 to 0.8 unit per kilogram of body weight per day, but glucose control was erratic and he had frequent episodes of hypoglycemia. The insulin was discontinued when he was 18 months old after it was noted that his blood glucose values remained in an acceptable range when it was omitted. However, he required low doses of insulin at the ages of 42 to 43 months, 48 to 54 months, and 78 to 84 months. Since then (he is 8.4 years old at the time of this writing), he has not required insulin, but his glycosylated hemoglobin values remain slightly elevated. Plasma C peptide was undetectable soon after birth, but later measurements were normal. Tests for anti-insulin and islet-cell antibodies were negative.

At the most recent follow-up visit, the patient was 8½ years old and 120 cm tall, with a weight of 26.2 kg and a head circumference of 51 cm. He had scoliosis but normal segmentation of the vertebrae and ribs. There were symmetric calcifications in the white matter behind the posterior horns of the lateral ventricles.

The second brother (Patient 51) was also delivered by cesarean section, in the 34th week of gestation, which again was complicated by preeclampsia. He weighed 1480 g, was 40 cm long, and had a head circumference of 30 cm. When he was one hour old, his blood glucose was 60 mg per deciliter (3.3 mmol per liter). At two and

From the Kinderhospital, Iburger Str. 187, D-49082 Osnabrück, Germany, where reprint requests should be addressed to Dr. von Mühlendahl.

three hours, it was 180 mg per deciliter (10.0 mmol per liter) and 300 mg per deciliter (16.6 mmol per liter), respectively. He was treated with insulin until the age of five years, during which time he had erratic glycemic control and frequent hypoglycemia. For the next 1.5 years, he received no insulin and had mild hyperglycemia, but insulin therapy had to be resumed at the age of 6½. He has never had diabetic ketoacidosis. Plasma C peptide was not detectable in infancy, and tests for anti-insulin or islet-cell antibodies were negative. When he was 5.4 years of age, acute lymphoblastic leukemia developed, which was treated successfully, resulting in complete remission.

At the time of the most recent follow-up visit, the patient was 6.8 years old and 98 cm tall, with a weight of 14.2 kg and a head circumference of 52 cm. His leukemia was still in remission. He had hemivertebrae of the 10th and 11th thoracic vertebrae and posterior fusion of the ribs at this level. There were some small areas of calcification in the white matter above the middle of the left lateral ventricle.

Both patients are severely retarded in their mental and motor development, having just reached a social age of 18 to 24 months at chronologic ages of 8 and 6 years. They speak only a few syllables. Both appear to hear normally. Because of ataxia and severe muscular hypotonia, they are unable to walk, and both have neurophysiologic evidence of progressive axonal neuropathy with demyelination. They have high foreheads; triangular faces; epicanthus; narrow lips; small, pointed teeth; and hyperopia. Both are positive for HLA-DR3 and DR4, having received DR3 from the father and DR4 from the mother.

Both brothers have hyperuricemia, as does their mother. This was detected when urate crystals were seen in the diapers, and phosphoribosyl-ATP pyrophosphatase hyperactivity was subsequently found.⁴ The mother has recurring episodes of gout. She also has glucose intolerance and had gestational diabetes during both pregnancies.

Non-insulin-dependent diabetes mellitus developed in the father at the age of 47 years. Both the mother's parents have non-insulin-dependent diabetes.

RESULTS

Transient Neonatal Diabetes Mellitus

Twenty infants had transient neonatal diabetes mellitus (Table 1). Fifteen of the 17 neonates for whom length of gestation and birth weight were reported were small for their gestational ages (Fig. 1). The diabetes in these 20 infants lasted 17 to 1914 days. Mental development was normal in eight children who had been followed for 7 to 19 years, and in eight other children who were younger (4 months to 4 years). Slight neurodevelopmental retardation was reported in a pair of twins (Patients 15 and 16). One patient (Patient 17) had seizures and a complex cardiac malformation. No patient is known to have had microangiopathy.

Transient Neonatal Diabetes Mellitus with Later Recurrence

Twelve girls and one boy had transient neonatal diabetes with later recurrence (Table 2). All 13 were small for their gestational ages (Fig. 1). The neonatal diabetes lasted 14 to 325 days (median, 120), and the period of remission 7 to 20 years (median, 13). There was slight mental retardation in a pair of twins (Patients 26 and 27), which might well have been due to

Table 1. Transient Neonatal Diabetes Mellitus with No Later Recurrence.*

PATIENT NO.	YEAR OF BIRTH	SEX	DURATION OF GESTATION	BIRTH WEIGHT	DURATION OF HYPERGLYCEMIA AND INSULIN DEPENDENCY		DURATION OF FOLLOW-UP	SOURCE
					wk	g		
1	1952	F	40	2410	17-540	(I)	40 yr	Wylie, ⁵ Hutchinson et al. ⁶
2	1961	M	40	3250	10-120	(H)	4 mo	Hesse ⁷
3	1962	F	32	1512	8-68	(I)	19 yr	Coffey and Womack, ⁸ Coffey and Killelea ⁹
4	1970	M	NA	2200	3-110	(I)	11 yr	Coffey and Killelea ⁹
5	1972	M	NA	2438	NA		5 yr	Personal communication†
6	1975	M	38	2000	2-60	(H)	4 mo	Sodoyez-Goffaux and Sodoyez ¹⁰
7	1976	F	41	2010	4-60	(I)	16 yr	Haschke and Hohenauer ¹¹
8	1979	M	38	1540	5-33	(I)	4 yr	Kuna and Addy ¹²
9	1980	F	38	1590	6-91	(H)	3 yr	Belmonte et al. ¹³
10	1982	M	40	2885	1-60	(H)	10 yr	Mail survey
11	1983	F	35	1260	2-53	(I)	8 yr	Mail survey
					6-1920	(H)		
					6-180	(I)		
					480-1920	(I)		
12	1983	F	36	1870	7-24	(H)	4 mo	Steigenberger ¹⁴
					12-24	(I)		
13	1984	F	37	1900	NA		3 yr	Personal communication†
14	1984	F	29	725	13-270	(H)	2 yr	Mail survey
15	1986	M	37	1861	6-90	(H)	5 yr	Nielsen ¹⁵
16	1986	M	37	1954	6-90	(H)	5 yr	Nielsen ¹⁵
17	1987	F	24	420	8-35	(H)	7 mo	Mail survey
					14-35	(I)		
18	1987	F	NA	NA	30-630	(H)	3 yr	Mail survey
19	1990	F	37	1920	5-120	(I)	2 yr	Mail survey
20	1991	M	36	1370	NA-30	(I)	NA	Personal communication†

*I denotes insulin dependency, H hyperglycemia, and NA not available.

†Data were obtained from the authors of a previous case report.

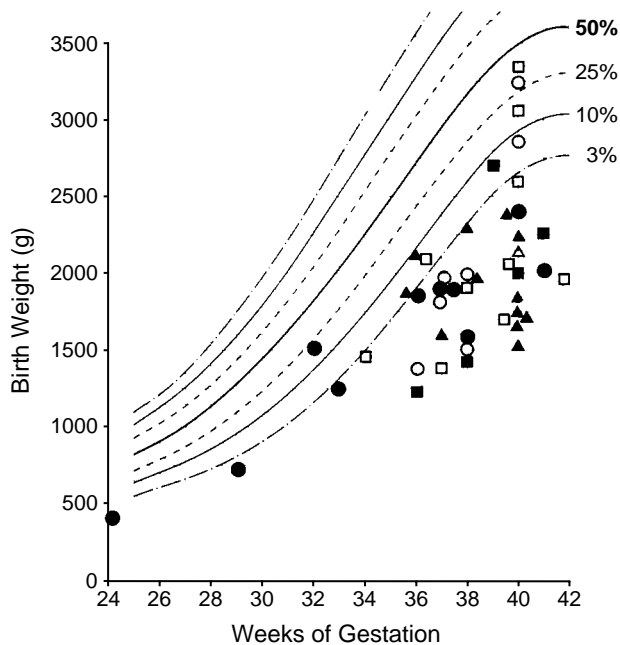


Figure 1. Birth Weight of 45 Patients with Neonatal Diabetes Mellitus.

The percentiles are those for normal girls from the study by Weller and Jorch.¹⁶ The third percentile for boys is higher by 20 g at 24 weeks of gestation, 125 g at 34 weeks, and 150 g at term. Closed symbols denote girls; open symbols, boys; circles, infants with transient neonatal diabetes; triangles, infants with transient neonatal diabetes with later recurrence; and squares, infants with permanent neonatal diabetes.

severe psychosocial problems of the family. One child (Patient 33) had seizures at the age of five years. One child (Patient 21) had necrobiosis lipoidica, and another (Patient 30) Tourette's syndrome. Two female patients (Patients 23 and 24) gave birth to normal chil-

dren, and one (Patient 28) fathered a boy who had transient neonatal diabetes mellitus (this boy was not included in this review). None of this group had microangiopathy.

Permanent Neonatal Diabetes Mellitus

In 8 of the 18 patients with permanent diabetes, the diabetes developed one to three days after birth (Table 3). Thirteen of the 15 neonates for whom data were available were small for their gestational ages (Fig. 1). Celiac disease later developed in two children (Patients 37 and 43), one of whom (Patient 37) died at the age of 15 years under unclear circumstances. Mental development was normal in nine children followed for long periods (8 to 32 years). Of the two with moderate mental retardation, one (Patient 46) was small for her gestational age but had a twin brother who was healthy and of normal weight at birth. Our two patients were severely retarded. Nothing is known about the intellectual development of five other patients.

One patient (Patient 38) had a capillary microaneurysm in the perimacular region of the right eye when he was 15 years old,^{34,35} but it then disappeared. There are no other reports of microangiopathy.

Wolcott-Rallison Syndrome

The Wolcott-Rallison syndrome is transmitted by autosomal recessive inheritance. So far, it has been described in four boys and two girls (Patients 52 through 57,¹⁻³ data not shown), belonging to three families. All the patients had persistent neonatal diabetes and either multiple epiphyseal (five patients) or spondyloepiphyseal (one patient) dysplasias. Two unrelated patients had progressive renal failure, and one had glomerulonephritis. Four of the patients have died, at the ages of 4, 11, 19, and 26 years. In all six patients, the onset of

Table 2. Children with Transient Neonatal Diabetes Mellitus with Later Recurrence.

PATIENT NO.	YEAR OF BIRTH	SEX	DURATION OF GESTATION	BIRTH WEIGHT	DURATION OF HYPERGLYCEMIA AND INSULIN DEPENDENCY*	DURATION OF FOLLOW-UP	AGE AT RECURRENCE	SOURCE
					wk			
21	1957	F	36	2130	30-51 (H)	21	18	Hutchinson et al., ⁶ Campbell et al. ¹⁷
22	1961	F	40	1540	14-280 (I)	22	12	Sweetnam and Sykes, ¹⁸ Briggs ¹⁹
23	1963	F	40	1850	14-36 (H)	28	20	Burland ²⁰
24	1963	F	40	1740	12-113 (H)	19	15	Coffey and Womack, ⁸ Coffey and Killelea ⁹
25	1967	F	40	2250	15-58 (H)	19	13	Levelon et al. ²¹
26	1967	F	38	1980	56-120 (H)	17	13	Mail survey
27	1967	F	38	2300	56-120 (H)	18	16	Mail survey
28	1970	M	40	2155	3-90 (H)	20	20	Schiff et al. ²²
29	1980	F	40	1700	1-180 (I)	13	13	Shield and Baum ²³
30	1980	F	40	2400	35-360 (I)	13	8	Weimerskirch and Klein ²⁴
31	1982	F	37	1600	2-NA (H)	7	7	Personal communication†
32	1982	F	40	1650	1-14 (I)	9	9	Geffner et al. ²⁵
33	1983	F	36	1900	5-180 (I)	10	10	Weimerskirch and Klein ²⁴

*H denotes hyperglycemia, I insulin dependency, and NA not available.

†Data were obtained from the authors of a previous case report.

diabetes was late (28th to 77th day; median, 43rd day). The two children for whom birth weights were reported were born at term and were not small for their gestational ages. The follow-up periods ranged from 4 to 26 years (median, 17).

Familial Cases

There were two pairs of twins (Patients 15 and 16 and Patients 26 and 27) and several pairs or triplets of siblings (Patients 50 and 51, as well as two siblings with Wolcott-Rallison syndrome from one family, and three siblings with the same syndrome from another family). Patients 3, 4, and 24 had the same father and different mothers. Insulin-dependent diabetes had developed in the mother of Patient 40 when she was 12 weeks old. Patient 28 was the father of a boy with transient neonatal diabetes. Insulin-dependent diabetes developed in the sister of Patient 45 at the age of 12 months; she also had celiac disease. The parents of our two patients had non-insulin-dependent diabetes.

Incidence

We now have information on 188 infants with neonatal diabetes obtained from a review of the literature and our survey. Estimates of the frequency of neonatal diabetes based on reports in the literature must necessarily be very imprecise. More useful for this purpose was our survey of German pediatric clinics and departments, which yielded 13 cases between 1977 and 1991. During this period, there were 9,300,000 births in Germany. About 60 percent of the questionnaires were answered, thus representing observations on nearly 6 million children. The incidence of neonatal diabetes would therefore be about 1 in 450,000. Since pediatricians

who had seen an infant with this disease would conceivably be more likely to have answered the questionnaire, the true incidence may be lower — perhaps 1 in 600,000 births.

DISCUSSION

We have described the combination of neonatal diabetes mellitus with phosphoribosyl-ATP pyrophosphatase hyperactivity in two brothers. Whether the presence of these two conditions is due to chance or to adjacent genetic defects is not known. Phosphoribosyl-ATP pyrophosphatase hyperactivity leads to gout and urolithiasis in early adulthood. The reports on children with this disorder from four families mention prenatal growth retardation, motor and mental retardation, ataxia, hypotonia, hearing impairment, and disturbed speech development, but not diabetes.

Forty-seven of the patients had neonatal diabetes with hyperglycemia requiring insulin therapy that began during the first month of life, and 10 additional infants had hyperglycemia that began between the 42nd and 85th days of life. We excluded all infants with transient hyperglycemia of less than two weeks' duration that could be attributed to such factors as cerebral trauma, hypoxemic cerebral lesions, cerebral hemorrhage, or meningitis and encephalitis.

Among infants with neonatal diabetes, some have permanent diabetes, others have remission of their diabetes and later recurrence, and still others have apparently permanent remission. Since diabetes may recur after a prolonged period, however, one should hesitate to consider a remission permanent, and neonatal diabetes should probably be considered as a prediabetic state. The two brothers described here are classi-

Table 3. Children with Permanent Neonatal Diabetes Mellitus.*

PATIENT NO.	YEAR OF BIRTH	SEX	DURATION OF GESTATION	BIRTH WEIGHT	AGE AT ONSET	DURATION OF FOLLOW-UP	SOURCE
			wk	g	days	yr	
34	1957	F	40	2000	28	36	Mattern and Schreier ²⁶
35	1960	M	40	3350	65	32	Brugsch ²⁷
36	1963	M	40	2050	8	2	Hesse ⁷
37†	1969	M	40	1700	21	15	Francois et al. ²⁸
38	1973	M	40	2600	3	20	Dorchy et al., ²⁹ Dorchy ³⁰
39	1976	M	38	1920	NA	15	Personal communication‡
40	1979	M	36	2100	5	13	Widness et al., ³¹ Cornblath and Schwartz ³²
41	1980	F	41	2260	5	9	Knip et al. ³³
42	1982	M	42	1970	3	10	Hanbler and Bartmann ³⁴
43†	1982	M	40	3080	8	10	Hattevig et al. ³⁵
44	1982	F	NA	2250	1	8	Mail survey
45	1985	M	29	NA	1	NA	Mail survey
46	1988	F	38	1430	2	NA	Mail survey
47	1989	F	28	NA	NA	NA	Personal communication‡
48	1990	F	39	2740	2	NA	Mail survey
49	1990	F	36	1220	14	3	Mail survey
50	1986	M	37	1390	1	8.5	Christen et al. ⁴
51	1988	M	34	1480	1	6.8	Christen et al. ⁴

*NA denotes not available.

†Patients 37 and 43 had celiac disease.

‡Data were obtained from the authors of a previous case report.

fied as having permanent diabetes, although each had remissions of their hyperglycemia.

Do the different long-term outcomes indicate that neonatal diabetes is more than one disorder? Neonatal diabetes has some similarities to insulin-dependent diabetes as it occurs in older children: heredity plays an important part, and HLA haplotypes typical for insulin-dependent diabetes may be present. Two brothers (Patients 50 and 51) had HLA-DR3 and DR4, and other patients had HLA-DR3 (Patients 31, 33, and 38) or DR4 (Patients 26 and 27).

On the other hand, at least half the patients did not appear to have the usual type of insulin-dependent diabetes that simply developed unusually early in life. Insulin-dependent diabetes is thought to be an autoimmune disease with a genetic predisposition, in which some causative factor initiates an autoimmune process that leads to destruction of the beta cells and insulin deficiency. It is unlikely that this process would not only begin but also become well-advanced in utero. Since only one mother had insulin-dependent diabetes herself, transplacental passage of maternal anti-islet-cell antibodies was probably not a factor affecting beta-cell function in most infants. Finally, permanent or prolonged remissions are very unusual in insulin-dependent diabetes but quite frequent in neonatal diabetes.

Many infants with neonatal diabetes were small for their gestational ages, and some were extremely small. One may speculate that intrauterine growth retardation may cause neonatal diabetes, and low birth weight may be associated with decreased beta-cell function in adults.³⁶ The possible importance of intrauterine growth retardation is supported by the occurrence of neonatal diabetes in one neonate (Patient 46) who had a twin brother (of unknown zygosity) whose birth weight was normal and who was not diabetic. The infants with onset of diabetes in the second and third month of life for whom we obtained data usually had normal birth weights (and permanent diabetes).

Our results indicate that among newborn infants with diabetes mellitus, the diabetes will be transient in about 50 percent of cases. The presence of HLA-DR3 and DR4 increases the likelihood of permanent diabetes, as does onset after the age of one month. The presence of the Wolcott-Rallison syndrome or phosphoribosyl-ATP pyrophosphatase hyperactivity appears to be associated with a poor prognosis with respect to remission of diabetes as well as to longevity and the occurrence of additional problems. Nevertheless, the overall prognosis for general health and normal intellectual development is usually good.

REFERENCES

1. Wolcott CD, Rallison ML. Infancy-onset diabetes mellitus and multiple epiphyseal dysplasia. *J Pediatr* 1972;80:292-7.
2. Goumy P, Maroteaux P, Stanesco V, Stanesco R, Labbe A, Menut G. Syndrome de transmission récessive autosomique, associant un diabète congénital et des désordres de la croissance des épiphyses. *Arch Fr Pediatr* 1980;37:323-8.
3. Stöß H, Pesch HJ, Pontz B, Otten A, Spranger J. Wolcott-Rallison syndrome: diabetes mellitus and spondyloepiphyseal dysplasia. *Eur J Pediatr* 1982;138:120-9.
4. Christen HJ, Hanefeld F, Duley JA, Simmonds HA. Distinct neurological syndrome in two brothers with hyperuricaemia. *Lancet* 1992;340:1167-8.
5. Wylie ME. A case of congenital diabetes. *Arch Dis Child* 1953;28:297-9.
6. Hutchinson JH, Keay AJ, Kerr MM. Congenital temporary diabetes mellitus. *BMJ* 1962;2:436-40.
7. Hesse H. Angeborener Diabetes mellitus bei zwei Vetteren. *Kinderarztl Prax* 1963;31:333-40.
8. Coffey JD Jr, Womack NC. Transient neonatal diabetes mellitus in half sisters. *Am J Dis Child* 1967;113:480-2.
9. Coffey JD Jr, Killelea DE. Transient neonatal diabetes mellitus in half sisters: a sequel. *Am J Dis Child* 1982;136:626-7.
10. Sodoyez-Goffaux F, Sodoyez JC. Transient diabetes mellitus in a neonate: evaluation of insulin, glucagon, and growth hormone secretion and management with a continuous low-dose insulin infusion. *J Pediatr* 1977;91:395-9.
11. Haschke F, Hohenauer L. Transitorischer Diabetes mellitus bei einem dysmorphen Neugeborenen. *Helv Paediatr Acta* 1978;33:385-92.
12. Kuna P, Addy DP. Transient diabetes mellitus: treatment with chlorpropamide. *Am J Dis Child* 1979;133:65-6.
13. Belmonte MM, Kupfert B, Goldman H, Schiffrin A. Diabète transitoire du nouveau-né: rapport d'un cas et revue du sujet. *Info-Diabete* 1985;3:1-4.
14. Steigenberger H. Transitorischer Diabetes mellitus des Neugeborenen. *Monatsschr Kinderheilkd* 1986;134:207-8.
15. Nielsen F. Transient neonatal diabetes mellitus in a pair of twins. *Acta Paediatr Scand* 1989;78:469-72.
16. Weller U, Jorch G. Aktuelle Perzentilenkurven für Körpergewicht, Körperlänge und Kopfumfang von Neugeborenen ab 25 SSW. *Monatsschr Kinderheilkd* 1993;141:665-9.
17. Campbell IW, Fraser DM, Duncan LJ, Keay AJ. Permanent insulin-dependent diabetes mellitus after congenital temporary diabetes mellitus. *BMJ* 1978;2:174.
18. Sweetnam WP, Sykes CGW. Congenital diabetes mellitus. *BMJ* 1962;2:671-2.
19. Briggs JR. Permanent non-insulin dependent diabetes mellitus after congenital transient neonatal diabetes. *Scott Med J* 1986;31:41-2.
20. Burland WL. Diabetes mellitus syndrome in the newborn infant. *J Pediatr* 1964;65:122-3.
21. Nivelon J-L, Badinand P, Fau M, Cotte M-F, Ruitton-Ugliengo A, Béthenod M. Hyperglycémie néonatale transitoire et idiopathique: observation avec étude de l'insuline plasmatique. *Pediatric* 1970;25:887-99.
22. Schiff D, Colle E, Stern L. Metabolic and growth patterns in transient neonatal diabetes. *N Engl J Med* 1972;287:119-22.
23. Shield JP, Baum JD. Is transient neonatal diabetes a risk factor for diabetes in later life? *Lancet* 1993;341:693.
24. Weimerskirch D, Klein DJ. Recurrence of insulin-dependent diabetes mellitus after transient neonatal diabetes: a report of two cases. *J Pediatr* 1993;122:598-600.
25. Geffner ME, Clare-Salzler M, Kaufman DL, Ting GS, Gottschalk ME, Schatz DA. Permanent diabetes developing after transient neonatal diabetes. *Lancet* 1993;341:1095.
26. Mattern H, Schreier K. Diabetes mellitus in den ersten beiden Lebensjahren. *Arch Kinderheilkd* 1964;170:243-56.
27. Brugsch H. Diabetes mellitus im Säuglingsalter. *Z Arztl Fortbild (Jena)* 1962;51:439-44.
28. Francois R, Hermier M, Jarlot B, Laubeuf JC, David L, Pouillaude JM. Le diabète de la première année. *Arch Fr Pediatr* 1972;29:941-56.
29. Dorchy H, Ooms H, Loeb H. Permanent neonatal diabetes mellitus: a case report with plasma insulin studies. *Z Kinderheilkd* 1975;118:271-81.
30. Dorchy H. Permanent neonatal diabetes mellitus: lack of diabetic complications after a 20-year follow up. *Eur J Pediatr* 1992;151:151.
31. Widness JA, Cowett RM, Zeller WP, Susa JB, Rubenstein AH, Schwartz R. Permanent neonatal diabetes in an infant of an insulin-dependent mother. *J Pediatr* 1982;100:926-9.
32. Hyperglycemia in the neonate. In: Cornblath M, Schwartz R. Disorders of carbohydrate metabolism in infancy. 3rd ed. Boston: Blackwell Scientific, 1992:225-46.
33. Knip M, Koivisto M, Käär ML, Puukka R, Kouvalainen K. Pancreatic islet cell function and metabolic control in an infant with permanent neonatal diabetes. *Acta Paediatr Scand* 1983;72:303-7.
34. Hanbler H, Bartmann P. Permanenter Diabetes mellitus des Neugeborenen. *Therapiewoche* 1984;34:1487-90.
35. Hattevig G, Kjellman B, Fällström SP. Congenital permanent diabetes mellitus and celiac disease. *J Pediatr* 1982;101:955-7.
36. Cook JT, Levy JC, Page RC, Shaw JA, Hattersley AT, Turner RC. Association of low birth weight with beta cell function in the adult first degree relatives of non-insulin dependent diabetic subjects. *BMJ* 1993;306:302-6.

CORRECTION

Neonatal Diabetes Mellitus

To the Editor: The data on neonatal diabetes mellitus reported by von Mühlendahl and Herkenhoff (Sept. 14 issue)¹ indicate that the causes of this rare condition are heterogeneous. Among the 57 infants, only 7 were known to have HLA haplotypes associated with autoimmune diabetes. In most of the cases, the cause was unknown, and several infants also had very rare genetic disorders. The authors, however, failed to mention some published reports of cases of neonatal diabetes in which a cause could be demonstrated or suggested. The causes included pancreatic aplasia, a congenital absence of the islets, and selective agenesis of β cells.²

In one of the cases involving selective agenesis of β cells, we demonstrated paternal isodisomy of chromosome 6 (i.e., the chromosome pair consisted of two copies of the same paternal chromosome instead of following the normal pattern of biparental inheritance),³ and Temple and colleagues found paternal isodisomy 6 in two neonates with transient diabetes.⁴ These findings suggest that a subgroup of cases of neonatal diabetes may result from anomalies of chromosome 6, with a mutation or imprinting (i.e., differential expression of a gene depending on the parent of origin) of a putative gene involved in β -cell development located on that chromosome. Parental imprinting may also explain some familial recurrences that do not follow mendelian rules of inheritance.⁴ From a practical standpoint, the detection of uniparental disomy of chromosome 6 in patients with neonatal diabetes may help identify a subgroup of patients in whom the disorder has a different pathogenicity and prognosis.

Marc J. Abramowicz, M.D.
Harry Dorchy, M.D.
Esther Vamos, M.D.
Erasme Hospital
B-1070 Brussels, Belgium

References

1. von Mühlendahl KE, Herkenhoff H. Long-term course of neonatal diabetes. *N Engl J Med* 1995;333:704-708.
2. Blum D, Dorchy H, Mouraux T, et al. Congenital absence of insulin cells in a neonate with diabetes mellitus and mutase-deficient methylmalonic acidemia. *Diabetologia* 1993;36:352-357.
3. Abramowicz MJ, Andrien M, Dupont E, et al. Isodisomy of chromosome 6 in a newborn with methylmalonic acidemia and agenesis of pancreatic beta cells causing diabetes mellitus. *J Clin Invest* 1994;94:418-421.
4. Temple IK, James RS, Crolla JA, et al. An imprinted gene(s) for diabetes? *Nat Genet* 1995;9:110-112.

To the Editor: There are two pieces of misinformation about the patient described in my case report (Patient 32 and reference 25 in the article by von Mühlendahl and Herkenhoff). First, the duration of hyperglycemia was from day 1 to week 14 (day 98) of life, not to day 14 of life, as indicated in the authors' Table 2. This duration of hyperglycemia is similar to that in the other patients in the group. Second, microalbuminuria subsequently developed in this patient, making the authors' statement that no patient in the group with transient neonatal diabetes and later recurrences had microangiopathy incorrect. (I was not contacted for follow-up information.)

Mitchell E. Geffner, M.D.
UCLA Medical Center
Los Angeles, CA 90095

The authors reply:

To the Editor: We thank Abramowicz et al., for calling our attention to the identification of paternal isodisomy of chromosome 6 in some cases of neonatal diabetes mellitus, and Dr. Geffner, for the correction and additional information about his patient. Further follow-up of the patients in our survey is under way and may well reveal that over time, more patients have microangiopathy.

Karl Ernst von Mühlendahl, M.D.
Heiner Herkenhoff, M.D.
Kinderhospital
D-49082 Osnabrück, Germany