Prematurity and Genetic Testing for Neonatal Diabetes

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abstract

BACKGROUND: Hyperglycemia in premature infants is usually thought to reflect inadequate pancreatic development rather than monogenic neonatal diabetes. No studies, to our knowledge, have investigated the prevalence of monogenic forms of diabetes in preterm infants.

METHODS: We studied 750 patients with diabetes diagnosed before 6 months of age. We compared the genetic etiology and clinical characteristics of 146 preterm patients born <37 weeks and compared them with 604 born ≥37 weeks.

RESULTS: A genetic etiology was found in 97/146 (66%) preterm infants compared with 501/604 (83%) born ≥37weeks, $P < .0001$. Chromosome 6q24 imprinting abnormalities (27% vs 12%, $P = .0001$) and *GATA6* mutations (9% vs 2%, $P = .003$) occurred more commonly in preterm than term infants while mutations in *KCNJ11* were less common (21 vs 34%, $P = .008$). Preterm patients with an identified mutation were diagnosed later than those without an identified mutation (median [interquartile range] 35 [34 to 36] weeks vs 31 [28 to 36] weeks, $P < .0001$). No difference was seen in other clinical characteristics of preterm patients with and without an identified mutation including age of presentation, birth weight, and time to referral.

CONCLUSIONS: Patients with neonatal diabetes due to a monogenic etiology can be born preterm, especially those with 6q24 abnormalities or *GATA6* mutations. A genetic etiology is more likely in patients with less severe prematurity (>32 weeks). Prematurity should not prevent referral for genetic testing as 37% have a potassium channel mutation and as a result can get improved control by replacing insulin with sulphonylurea therapy.

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Dr Besser conceptualized and designed the study, performed the statistical analysis, and drafted and revised the initial manuscript; Drs Flanagan, Mackay, and Temple performed mutational analysis of samples and reviewed and revised the manuscript; Dr Shepherd coordinated the clinical data collection and reviewed and revised the manuscript; Dr Shields performed statistical analysis for the article and reviewed and revised the manuscript; Dr Ellard acquired the neonatal diabetes data set, performed mutational analysis of samples, and reviewed and revised the manuscript; Dr Hattersley acquired the neonatal diabetes data set, designed the study, interpreted the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Neonatal diabetes that presents in the first 6 months should be correctly diagnosed as the molecular genetic etiology defines the optimum lifelong management. Hyperglycemia is common in markedly premature neonates and usually rapidly remits without long-term treatment.

WHAT THIS STUDY ADDS: Patients with neonatal diabetes due to a monogenic etiology can be born preterm. A genetic cause is more likely in those born with less severe prematurity (gestation >32 weeks). Prematurity should not prevent referral for genetic testing.

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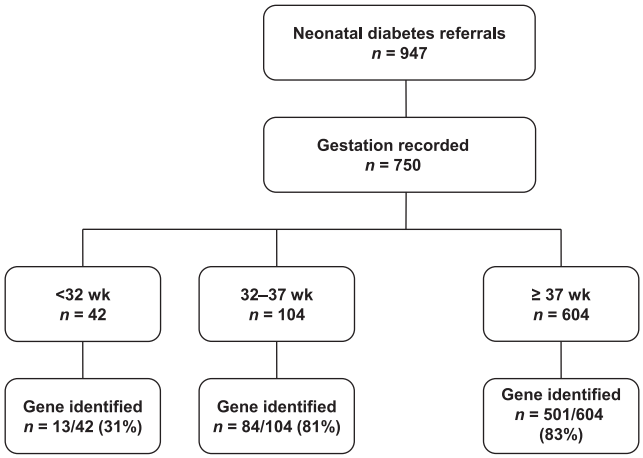

FIGURE 1
Number of patients with neonatal diabetes diagnosed <26 weeks referred for genetic testing according to gestation.

Prematurity (gestation <37 weeks) affects up to 12% of all births,[1] and hyperglycemia is a common complication usually attributed to an immature pancreas, insulin resistance, and abnormal glucose homeostatic mechanisms.[2,3] The risk of hyperglycemia is negatively associated with gestational age and birth weight, with the highest prevalence (up to 88%) seen in extremely low birth weight (<1 kg) preterm infants (<30 weeks) and those receiving intravenous glucose or parenteral nutrition, usually within the first week after birth.[4–9]

Neonatal diabetes, a rare (~1:200 000 live births)[10,11] genetically heterogeneous monogenic form of diabetes, may also present in the days and weeks after birth, and almost always before 6 months of age.[12–15] Approximately 50% of patients have heterozygous activating mutations in the *KCNJ11* and *ABCC8* genes encoding the adenosine triphosphate-sensitive potassium channel subunits, and in the vast majority of cases insulin injections can be successfully replaced with sulphonylurea tablets, making a correct genetic diagnosis crucial.[15–17]

The hyperglycemia seen in preterm infants and in patients with neonatal diabetes due to a monogenic cause may be difficult to discriminate. Both groups of patients can present shortly after birth and are associated with reduced birth weight. Neonatal diabetes may affect gestational age and so a percentage of patients could present prematurely, or certain mutations may result in premature birth. No studies have investigated patients with both permanent and transient neonatal diabetes who were born prematurely. We aimed to assess the clinical characteristics and genetic etiology of preterm patients with neonatal diabetes.

METHODS

Patients

We examined the Exeter International Cohort of 947 patients with neonatal diabetes, defined as hyperglycemia presenting <26 weeks of age, who were referred for genetic testing to the Department of Molecular Genetics at the Royal Devon & Exeter National Health Service Foundation Trust, Exeter, United Kingdom, before July 2012. The 750 (79%) patients who had a gestational age provided were included in the analysis (Fig 1). A mutation was classified as pathogenic if it was a known cause or highly likely to be pathogenic on the basis of the mutation characteristics, cosegregation in the family, and other clinical features consistent with that molecular diagnosis. Patients were recorded as not having an identified mutation if they tested negative for at least the 3 commonly occurring causes of neonatal diabetes: *KCNJ11*, *ABCC8*, and *INS* mutations.

Genetic Analysis

In all patients the *KCNJ11*, *ABCC8*, and *INS* genes were sequenced as previously described.[13,18] Methylation analysis of the chromosome 6q24 region, that causes transient neonatal diabetes, was undertaken in all patients whose diabetes had entered remission and in patients who were younger than 6 months at the time of referral for genetic testing. The *EIF2AK3*, *NEUROD1*, *RFX6, GCK, FOXP3, SLC19A2, GLIS3, PDX1, PTF1A, NEUROG3, HNF1B,* and *BSCL2* genes were sequenced by using standard methods in patients when testing was indicated by the phenotype or genetic information revealing homozygosity over the region of the gene (methods available on request).

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all patients, with parental consent given on behalf of children.

Statistical Analyses

Data were not normally distributed so nonparametric analysis was used. Patients were coded as preterm (born <37 completed weeks' gestation) or term (≥37 completed weeks' gestation). Birth weight was converted into gestation and gender adjusted SD scores (SDS) according to UK preterm growth charts.[19]

Characteristics of preterm and term infants with a confirmed monogenic cause for their diabetes, and preterm

infants with and without an identified mutation were assessed by using the Mann-Whitney *U* test for continuous variables not normally distributed (age of diagnosis, birth weight, gestation, and time to referral) and the χ^2 test for categorical data (gender, gene affected). Where expected frequencies of mutations were <5, the Fisher's exact test was used.

Gestation was split into the following 4 groups on the basis of the degree of prematurity: very preterm (<32 completed weeks, moderately preterm [33 to 36 completed weeks], term [37 to 40 completed weeks], and term plus [>40 weeks]).[20] The association between gestation and both birth weight and birth weight SDS was assessed by using the Jonckheere-Terpstra Test for trend.

Statistical analysis was performed by using SPSS version 15 software (IBM SPSS Statistics, IBM Corporation), and a probability level of $P < .05$ was assumed statistically significant.

RESULTS

Patient Characteristics

One hundred forty-six of 750 (19.4%) patients were born preterm, of which 104/750 (13.8%) patients were moderately preterm (33 to 36 completed weeks) and 42/750 (5.6%) very preterm (<32 completed weeks; Fig 1). A genetic cause was identified in 598/750 (79.7%) infants, of which 97/598 (16%) were preterm.

Characteristics of preterm and term infants with a monogenic cause for their diabetes are summarized in Table 1. Ninety-seven of 146 (66%) preterm infants had a defined genetic etiology for their diabetes, which was a lower percentage than those born ≥37weeks (501/604 [83%], $P < .0001$; Table 2). This was predominantly because of 42 patients referred with gestation <32 completed weeks, of which only 13/42 (31%) had a monogenic cause for their diabetes. If these very preterm patients were removed from the analysis, there was no difference in the proportion of preterm and term patients with a monogenic cause for their diabetes (84/104 [81%] vs 501/604 [83%], $P = .59$).

Preterm infants with a mutation compared with patients born at term, presented earlier (age of diagnosis: 1 [0.1 to 4] vs 6 [2 to 11] weeks, $P < .0001$), had a higher birth weight SDS (−1.27 [−2.27 to −0.43] vs −1.76 [−2.59 to −0.98], $P < .001$), and were referred for genetic testing earlier (19 [4 to 212] vs 73 [7 to 473] weeks, $P = .003$; Table 1).

Which Genetic Mutations Are Seen in Preterm Infants?

The genetic mutations seen in premature and term patients are shown in Table 2. Methylation defects at chromosome 6q24 and *GATA6* mutations occurred more commonly in preterm than term infants (*6q24*: 27% vs 12%, $P = .0001$; *GATA6*: 9% vs 2%, $P = .003$). Mutations in *KCNJ11* were less common in preterm infants (21% vs 34%, $P = .008$), but there was no difference in *ABCC8* mutations (16% vs 18%, $P = .73$).

TABLE 1 Characteristics of Preterm and Term Infants With Neonatal Diabetes and With a Known Genetic Etiology

Patient Characteristic	Gestation, wk		*P*
	<37, *n* = 97	≥37, *n* = 501	
n (% boys)	51 (53)	282 (56)	.61
Age at diagnosis, wk	1.0 (0.1 to 4.0)	6.0 (2.0 to 11.0)	<.0001
Birth weight, g	1730 (1450 to 2200)	2600 (2230 to 3000)	<.0001
Birth weight, SDS	−1.27 (−2.27 to −0.43)	−1.76 (−2.59 to −0.98)	<.0001
Birth weight, centile	10 (1.2 to 34)	3.9 (0.5 to 16)	.002
Gestation, wk	35 (34 to 36)	40 (38 to 40)	<.0001
Time to referral from diagnosis, wk	19 (4 to 212)	73 (7 to 473)	.003

Data presented as median (interquartile range) unless otherwise stated. SDS and percentile birth weights were calculated according to UK-World Health Organization preterm growth charts. Missing for birth weight (preterm, *n* = 5; term, *n* = 18), time to referral (term, *n* = 8).

TABLE 2 Genetic Etiology of Preterm and Term Infants With Neonatal Diabetes

	Gestation, wk		*P*
	<37, *n* = 146	≥37, *n* = 604	
n (%) with a confirmed mutation	97/146 (66)	501/604 (83)	<.0001
Genetic cause	*n* = 97	*n* = 501	
KCNJ11	20 (21)	172 (34)	.008
ABCC8	16 (16)	90 (18)	.73
INS	9 (9)	80 (16)	.09
6q24	26 (27)	60 (12)	.0001
EIF2AK3	4 (4)	43 (9)	.14
GATA6	9 (9)	12 (2)	.003[a]
GCK	6 (6)	14 (3)	.12[a]
FOXP3	2 (2)	9 (2)	.70[a]
SLC19A2	0	7 (1)	.61[a]
GLIS3	2 (2)	3 (0.6)	.19[a]
PDX1	0	4 (0.8)	>.99[a]
PTF1A	0	2 (0.4)	>.99[a]
NEUROG3	1 (1)	1 (0.2)	.30[a]
NEUROD1	1 (1)	1 (0.2)	.30[a]
RFX6	1 (1)	0	.16[a]
HNF1B	0	1 (0.2)	>.99[a]
BSCL2	0	1 (0.2)	>.99[a]
IER31P1	0	1 (0.2)	>.99[a]

Differences between groups were calculated by using Mann-Whitney U and χ^2 tests.
[a] Where expected frequencies <5, Fisher's exact test was used.

No difference was seen between preterm and term infants for all other mutations ($P > .1$).

Can Clinical Characteristics Identify Which Preterm Infants Are More Likely to Have Neonatal Diabetes?

The clinical characteristics seen in premature patients <37 completed weeks' gestation with and without mutations are shown in Table 3. Preterm infants with a monogenic form of diabetes were born later than those without an identified mutation (gestation 35 [33 to 36] vs 31 [29 to 36] weeks, $P < .0001$). In keeping with this the birth weight was greater (1730 [1450 to 2200] vs 1340 [820 to 1770], $P < .0001$), but there was no difference after correction for gestational age birth weight SDS (−1.28 [−2.27 to −0.43] vs −1.06 [−1.98 to −0.20], $P = .48$). There was no difference in the age at presentation (1 [0.1 to 4] vs 0.7 [0.1 to 3.5] weeks, $P = .99$), or gender (% boys, 54 vs 63, $P = .27$). There was an insignificant trend for time to referral to be longer in preterm patients with a monogenic cause compared with those where a mutation was not found (19 [4 to 212] vs 8 [4 to 42] weeks, $P = .10$). Only 1 patient was diagnosed with a mutation that at the time of referral for genetic testing was under a corrected gestational age of 34 completed weeks. There were 12 patients without a mutation who were referred with a corrected gestational age younger than 34 completed weeks.

TABLE 3 Clinical Characteristics of Preterm Infants (Gestation <37 wk) With Neonatal Diabetes With ($n = 97$) and Without ($n = 49$) an Identified Genetic Mutation

Characteristic	Gene Status, $n = 146$		P
	Mutation Identified	No Mutation Identified	
n (%)	97 (66)	49 (34)	—
n (% boys)	51 (54)	31 (63)	.27
Gestation, wk	35 (34 to 36)	31 (28 to 36)	<.0001
Age at diagnosis, wk	1.0 (0.1 to 4.0)	0.7 (0.1 to 3.5)	.99
Birth weight, g	1730 (1450 to 2200)	1340 (820 to 1770)	<.0001
Birth weight, SDS	−1.28 (−2.27 to −0.43)	−1.06 (−1.98 to −0.20)	.48
Birth weight, centile	10 (1.2 to 34)	14 (2 to 42)	.49
Time to referral from diagnosis, wk	19 (4 to 212)	8 (4 to 42)[a]	.10

Data presented as median (interquartile range) unless otherwise stated.
[a] Missing data, $n = 3$.

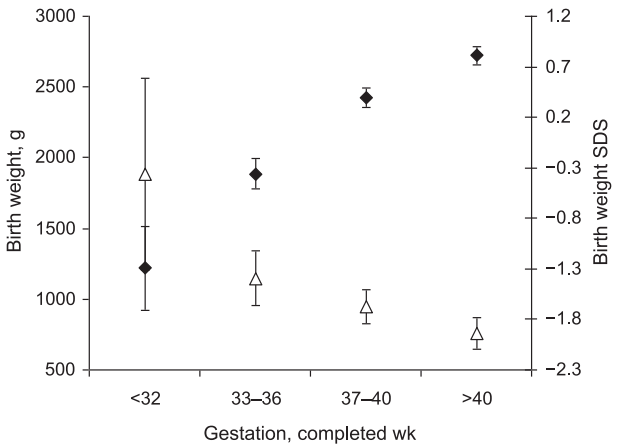

FIGURE 2
Relationship between gestation and birth weight in patients with a proven genetic etiology of their neonatal diabetes.

Impact of Gestation on Birth Weight in Patients With Neonatal Diabetes

In the preterm patients with an identified mutation, gestation-adjusted birth weight SDS was higher than in those born at term (−1.27 [−2.27 to −0.43] vs −1.76 [−2.59 to −0.98], $P < .0001$). The impact of gestational age on both birth weight and birth weight adjusted for gestation and gender (birth weight SDS) in patients with an identified mutation is shown in Fig 2. Birth weight increased with gestational age ($P < .0001$), but birth weight SDS decreased with gestational age ($P < .0001$; Fig 2).

DISCUSSION

In this study of 750 patients with neonatal diabetes, we have demonstrated that patients with a monogenic etiology can be born premature. Although mutations were less common in children with severe prematurity (<32 completed weeks' gestation), probably due to pancreatic immaturity causing hyperglycemia, it is important to note that a monogenic diagnosis was still made on 31% of patients in this group.

Prematurity in Neonatal Diabetes

We found 66% of preterm patients with neonatal diabetes in our cohort with a genetic diagnosis and conversely 16% of patients with a genetic diagnosis were born prematurely. This suggests that premature delivery may be more frequent in patients with monogenic neonatal diabetes than the 12% seen in the normal population.[1] There are only 2 large independent series to compare this with and both have limited information on gestational age. In an American series of neonatal diabetes in patients diagnosed with diabetes <12 months of age ($n = 77$), at least 1 of the 23 patients was born prematurely.[21] In a series by

the French Neonatal Diabetes Study Group (n = 79), 2 of the 15 patients with *ABCC8* mutations were born premature,[22,23] whereas none of the 9 patients with *KCNJ11* mutations or 7 patients with *INS* mutations (where recorded) were born premature.[23] It is unclear whether the 5 preterm patients included in the original French series had abnormalities in chromosome 6q.[24] More recently, in a small study of 15 patients born under 32 weeks with transient hyperglycemia, 2 patients were identified as having a monogenic etiology (*KCNJ11* mutation, 6q24 abnormality).[25] Similar to our study, these 2 patients presented earlier than those without a mutation. It is unclear whether the 13 patients without an identified mutation had a monogenic etiology because genetic testing was limited to 6q24 abnormalities, *INS, KCNJ11*, and *ABCC8* gene mutations. In our study, we identified 12 different causes of monogenic etiology in preterm infants born under 37 weeks.

Genetic Etiology of Neonatal Diabetes in Preterm Infants

The high proportion of premature infants with 6q24 abnormalities is similar to recent reports by Temple et al.[26] Our finding of a higher proportion of *GATA6* mutations in preterm infants has not been reported previously, but is not unexpected. One feature common to both is severe intrauterine growth retardation,[27,28] which may result from a reduction in third trimester insulin mediated fetal growth.[18,29] Prematurity may result from early elective delivery due to poor fetal growth. Furthermore, *GATA6* is a key transcription factor involved in multiple organ development, including the endocrine and exocrine pancreas.[27] Critical cardiac anomalies have been reported in patients with mutations in *GATA6* and it is possible that prematurity is the result of spontaneous or elective delivery due to concerns with cardiac functioning, although we do not have any data to test this hypothesis.[27] This may explain the finding in our data that preterm patients who have a genetic etiology identified are referred for testing sooner than term patients.

Clinical Differences to Aid Genetic Referral

It is not possible to accurately identify patients who are born prematurely with monogenic neonatal diabetes on the basis of clinical features alone. Although hyperglycemia in the very preterm infant (<32 completed weeks) makes a monogenic cause less likely, it cannot be excluded as 31% of patients in this group had a genetic cause identified. Within the group of preterm infants born under 37 weeks, 36/97 (37%) had a potassium channel mutation, which would radically alter the optimum treatment. This means that prematurity should not deter clinicians from referring preterm patients with hyperglycemia for genetic testing.

In our cohort, preterm infants with an identified mutation were referred earlier than those born at term; however, we do not have any data about the duration of hyperglycemia before genetic referral, or the reason for referral. Hyperglycemia secondary to prematurity would not be expected to persist as the immature pancreas, coupled with abnormal glucose homeostasis, the need for parenteral nutrition, steroid administration and stress, including sepsis should resolve with time. Remitting hyperglycemia may also occur in neonatal diabetes due to a genetic cause (transient neonatal diabetes mellitus), whereas in permanent neonatal diabetes mellitus the hyperglycemia will persist. Resolution of hyperglycemia therefore may reflect improved maturity or natural remission due to a monogenic cause, but persistence of hyperglycemia is likely to reflect a monogenic cause of neonatal diabetes. However, patients with an identified mutation did not have a longer time to referral.

Impact of Gestation on Birth Weight

Our results revealing reduced birth weight in patients with neonatal diabetes is well-described.[30] This is attributed to hypoinsulinemia during the third trimester of pregnancy when insulin-stimulated fetal growth should normally occur. This is supported by our data that demonstrate that birth weight SDS is lower with increasing gestational age.

Study Limitations

Our data have a strong referral bias. We were only able to include patients who were referred to our center, so we are unable to say how often the hyperglycemia seen in premature infants is due to a monogenic cause. It is likely that a large number of patients with hyperglycemia due to prematurity were not referred for genetic testing. It is likely that, in the absence of sepsis, term infants are referred for genetic testing more commonly as there is no underlying prematurity to explain the hyperglycemia. In addition, some term as well as preterm infants with transient hyperglycemia may not have been referred for genetic testing. This group of patients may represent at a later stage with diabetes mellitus, and depending on the age at presentation, they may be misdiagnosed as having either type 1 diabetes if they are young and/or slim, or type 2 diabetes, if they are older or obese. This would result in inappropriate management. In addition, it may not raise suspicion of monogenic diabetes within other family members. These limitations mean that the prevalence of monogenic diabetes in preterm infants is unknown, and is likely to be overestimated in this cohort. Prospective studies are needed to determine the prevalence of neonatal

diabetes in preterm infants with hyperglycemia.

We are only able to test for known genetic causes of neonatal diabetes, and it is likely that there are more unknown causes. In the patients without a genetic cause, we have not systematically screened for all known genetic causes of neonatal diabetes, so it is possible that there are more monogenic cases in the cohort currently without a genetic diagnosis.

We were unable to determine the duration and severity of hyperglycemia in our cohort. Further studies are needed to determine whether the duration or degree of hyperglycemia can identify when hyperglycemia is likely to be due to a monogenic cause.

Implications

Our results indicate that prematurity should not exclude a diagnosis of neonatal diabetes. As improved survival of extremely low birth weight preterm neonates continues, hyperglycemia will become more common in this age group. It is likely that there is an under referral of preterm hyperglycemic infants for genetic testing, particularly as some early genetic studies excluded patients born prematurely.

The 37% of preterm patients with adenosine triphosphate-sensitive potassium channel mutations is clinically important as these patients are likely to be successfully transferred from insulin onto oral sulphonylureas with an improvement in glycemic control.[16,17] Identifying neonatal diabetes due to other genetic causes is also recommended to provide prognostic information on disease progression, screening for comorbidities, and genetic counseling for affected future pregnancies.

Recommendations

Because only 13/750 (<2%) patients had a monogenic cause identified and were born severely preterm, we recommend genetic referral of preterm patients with hyperglycemia if they are born after 32 completed weeks in whom septicemia is not present. Testing before this gestational age should probably be limited to those patients in whom hyperglycemia persists until their corrected gestational age is 32 weeks.

We report that patients with monogenic neonatal diabetes can be born premature and hence prematurity should not prevent referral for genetic testing.

ABBREVIATION

SDS: SD score

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