Diabetes Presentation in Infancy: High Risk of Diabetic Ketoacidosis

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Diabetes in childhood has been associated with increased morbidity and mortality, but the risks for diabetes in infancy remain unclear. Cases with onset of hyperglycemia in the first 6 months of life consist predominantly of monogenic diabetes, whereas type 1 autoimmune diabetes accounts for the majority of cases beyond this threshold. Regardless of etiology, diabetes symptoms tend to be difficult to recognize in an infant, putting patients at increased risk for delays in diagnosis, which may lead to higher blood glucose levels and diabetic ketoacidosis (DKA) at presentation. Here, we report a high degree of morbidity among a cohort of subjects with infancy-onset diabetes.

We examined diagnosis records from 88 cases with diabetes onset ≤13 months of age collected through the University of Chicago Monogenic Diabetes Registry (1). We assessed laboratory values and sign/symptoms, and if a causal mutation for diabetes was detected, participants were subdivided by similar mutation subtypes. Data were managed using REDCap electronic data capture tools and analyzed using Stata version 14 (StataCorp, 2015).

The majority of participants were male (*n* = 46, 52%), Caucasian (*n* = 55, 63%), and living in the United States (*n* = 83, 94%). There was no significant difference across mutation subtypes based on socioeconomic status ($P = 0.19$), race/ethnicity ($P = 0.36$), or sex ($P = 0.07$). *KCNJ11*-related diabetes was the most common form of infancy-onset diabetes (37.5%, *n* = 33), followed by "Unknown" (likely type 1 diabetes) (21.6%, *n* = 19); 14% (*n* = 12) had transient neonatal diabetes. Median age at diabetes diagnosis was 10.4 weeks and was significantly different by mutation subtype (Table 1). When grouped into permanent versus transient diabetes, diagnosis age was significantly lower in the transient group (median 15.2 weeks vs. 0.43 weeks, $P < 0.001$). The most commonly reported signs/symptoms were polyuria (*n* = 32), tachypnea (*n* = 31), flu-like symptoms (*n* = 30), tiredness/weakness (*n* = 28), dehydration (*n* = 27), and "not acting right" (*n* = 26). Blood glucose, pH, bicarbonate, HbA_{1c}, and DKA were dependent on mutation subtype (Table 1). Overall frequency of DKA was 66.2% (Table 1), and odds of DKA increased with age at diagnosis (odds ratio per 1 month increase 1.23 [95% CI 1.04, 1.45]).

In this study—the largest of its kind—DKA was more frequent than in other early-onset U.S. studies (2,3) or other cohorts of patients with neonatal diabetes (4,5). One reason for this may be a delay in diagnosis, which is reflected in the increased likelihood of DKA at a later age of diagnosis found in our study. This delay may be related to the challenge of diagnosing diabetes in infants who cannot communicate symptoms and in whom polydipsia and polyuria may not be readily apparent and could even be reassuring to clinicians. Presentation characteristics were different by mutation subtype, therefore this information (in addition to genetic testing) may help to guide providers when making clinical decisions. Continuing to educate pediatric providers about the many ways that infants can present with diabetes may help to diagnose cases more efficiently and ultimately decrease the frequency of DKA at diagnosis. Further study is needed to develop effective strategies to reduce morbidity and mortality in this vulnerable population.

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Table 1—Details of diabetes diagnosis by mutation subtype

	*KCNJ11/ABCC8**	*INS/EIF2AK3**	6q24*	*FOXP3/IL2RA**	*GATA6/PDX1**	Unknown (likely T1D)*	Total*	*P* value
Number of participants, *n* (%)	41 (46.6)	13 (14.8)	10 (11.4)	3 (3.4)	2 (2.3)	19 (21.6)	88 (100)	
Current age, years	9.5 (5.2–14)	5.3 (2.5–8.6)	3.7 (1.4–5.4)	3.3 (3.2–6.6)	3.2 (2.2–4.2)	10.9 (6.7–17.9)	7.7 (4.1–14.0)	
Age at diagnosis, weeks	9.6 (6.1–18.3)	10 (6.1–17.4)	0.4 (0–0.9)	14.8 (0–22.2)	9.1 (0–18.3)	42.6 (37.4–50.4)	10.4 (5.2–26.5)	<0.001†
Glucose, mg/dL‡	716.5 (563–870)	435 (319–625)	408 (300–502)	920 (342–1,600)	411 (355–467)	736 (526–840)	618 (477–800)	<0.001†
pH§	7.07 (6.87–7.26)	7.41 (7.4–7.43)	7.43 (7.39–7.46)	6.95 (6.9–7.0)	7.11 (6.9–7.31)	7.08 (7.0–7.27)	7.08 (6.98–7.31)	0.02†
Bicarbonate, mmol/L‖	6.0 (4.6–11.0)	16.4 (15.0–25.0)	21.1 (20.0–21.8)	13.0 (6.0–20.0)	16.0 (7.0–25.0)	5.0 (4.0–10.4)	7.0 (5.0–18.8)	0.005†
HbA_{1c}, % [mmol/mol]¶	12.0 [108] (9.3–13.6) ([78–125])	9.9 [85] (8.5–10.9) ([69–96])	NA	4.9 [30]	NA	8.8 [73] (6.9–9.8) ([52–84])	9.9 [85] (8.3–12.2) ([67–110])	0.04†
DKA, *n* (%)#	26 (78.8)	3 (30)	0 (0)	3 (100)	1 (50)	14 (87.5)	47 (66.2)	<0.001†

All data presented as median (interquartile range) unless otherwise specified. T1D, type 1 diabetes; NA, not available. *In most cases, the mutation subtype was not reported in the medical record but rather was available for each case through the Monogenic Diabetes Registry data. Mutation subtypes were grouped according to functional similarities. All participants in the "Unknown" category did not have an identifiable monogenic cause of diabetes at the time of data analysis. Some of these participants had positive diabetes autoantibodies, and thus likely had autoimmune type 1 diabetes. "Total" category represents pooled participants. †Statistically significant by Wilcoxon rank sum test, Kruskal-Wallis test, or Fisher exact test. Because of limited sample sizes, pairwise comparisons were not performed. ‡Data available from 73 participants. §Data available from 49 participants. ‖Data available from 58 participants. ¶Data available from 27 participants; HbA_{1c} < 6 months are underestimated owing to fetal hemoglobin. #Data available from 71 participants.

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