Extremely Early Onset Type 1 Diabetes in the Emergency Setting: A Unique Presentation of a Common Childhood Onset Disease

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ABSTRACT

Introduction: As the prevalence of type 1 and type 2 diabetes continues to increase, hospitals have developed protocols for managing its many complications, particularly diabetic ketoacidosis. However, extremely early onset type 1 diabetes, defined as onset at age < 2 years old, remains a diagnostic challenge to the community clinician.

Case Presentation: We report a case report of a 19-month-old female thought to have acute on chronic constipation who presented to our pediatric emergency department and was subsequently found to be in diabetic ketoacidosis.

Discussion: This case emphasizes the importance of maintaining a high suspicion for this potentially lethal disease presentation, as well as the variety of symptoms that can occur with it.

Conclusions: The limited communicative ability of the pediatric population often results in unclear or vague initial complaints at disease onset. This has led to a paucity of literature and knowledge surrounding the diagnosis of extremely early onset type 1 diabetes, making delayed diagnosis and its associated complications commonplace.

INTRODUCTION

Diabetes is a disorder in which the body does not produce enough insulin or does not respond appropriately to insulin, in turn causing the blood glucose level to be abnormally high.[1] As diabetes has become increasingly common over the past decade, an abundance of research has surfaced.[2-4] A robust portion of this research is devoted to determining the etiology of the disease, of which both genetic and environmental factors have been implicated.[1-3] Although type 1 diabetes classically has been considered a disease of childhood and type 2 a disease of adults, there has been an uptrend in the prevalence of both across each age group.[2-3] Despite this, among those diagnosed with type 1 diabetes, it is most frequently discovered in a biphasic distribution: from the ages of 4 to 7 and later, from the ages of 10 to 13 years.[2-4] Although diabetes is associated with several comorbidities as well as mortality in the long term, the challenges of a timely diagnosis in the pediatric population, coupled with the high prevalence of diabetic ketoacidosis (DKA) at initial presentation (30%) in this group, has prompted the development of several guidelines and protocols at major children's hospitals in an attempt to quickly identify and treat this condition.[5,6]

DKA is defined as diabetes with the following features: hyperglycemia (blood glucose > 200 mg/dL), metabolic acidosis (serum bicarbonate < 18 mmol/L or venous pH < 7.3), and ketosis (ketones in the urine or blood).[7] A 2022 systematic review revealed the following major risk factors as being associated with an increased likelihood that a patient would present in DKA: age < 2 years at onset/diagnosis, being part of an ethnic minority population, delayed diagnosis/missed diagnosis, and presenting during the COVID-19 pandemic.[8] In particular, it is postulated that younger children are at increased risk of delayed diagnosis and, thus, DKA at presentation due to the inability or difficulty of obtaining a concrete clinical history – especially pertaining the classic triad of polyuria, polydipsia, and polyphagia (often with associated weight loss).[10-12] Alternatively, others have hypothesized that the higher rate of DKA at time of diagnosis in this population is due to a more severe autoimmune phenotype, as evidenced by higher titers of multiple diabetes-associated antibodies as well as lower c-peptide levels at diagnosis.[13]

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TableE4: . Patient's Vital Sign Trends Throughout Emergency Department (ED) Course and at Time of Discharge

	Heart Rate[a] (RR 90-140 bpm)	Blood Pressure[a] (RR 86-106/42-63 mmHg)	Respiratory Rate[a] (22-37 rpm)	Temperature (axillary)	SpO_2
On presentation to the ED	138	135/90	36	36 °C (96.8 °F)	100%
After 1st intravenous fluid bolus	128	109/78	24	N/A	100%
After 2nd intravenous fluid bolus	124	101/51	31	N/A	100%
At time of discharge from hospital	116	104/62	22	36.4 °C (97 °F)	100%

Abbreviations: RR, references ranges; bpm, beats per minute; rpm, respirations per minute; mmHg, millimeters of mercury; SpO_2, peripheral oxygen saturation.
[a]RRs are provided based on Pediatric Advanced Life Support (PALS) through the American Heart Association (AHA) 2020.
Consider individual's baseline values, as aberrations are expected depending on illness condition, stress

Although the most common presenting complaint at initial type 1 diabetes diagnosis in the overall pediatric population is polyuria (92% in 1 study), the most common complaint in children < 2 years old with new onset type 1 diabetes is poorly defined.[7]

Given the rarity of this early life diagnosis, literature is relatively sparse. However, Quinn et al noted that parents frequently brought their young children to medical attention for nonspecific complaints, including abdominal pain, dehydration, and fatigue.[14] Further, the classic symptoms of hyperglycemia, such as enuresis, polydipsia, polyuria, polyphagia, candidiasis, and fatigue, were reported less frequently in patients less than 2 years of age compared to those from 2 to 4 years old and 4 to 6 years old.[14] Several studies suggest this is due to limited communicative ability, diaper wearing, and shorter duration of symptoms prior to progression to significant metabolic derangement and critical illness.[11,14-15]

In addition to delayed diagnosis, the severity of clinical status at presentation is often worse due to the overall higher metabolic rate of these young patients, exacerbating the effects of dehydration, as well as their immature cerebral autoregulatory systems, predisposing them to cerebral edema, a feared and often fatal complication of DKA.[9-11,14-15] Despite the rarity of extremely early onset type 1 diabetes, the high risks associated with delayed or missed diagnosis make it imperative for the emergency medicine provider to remain vigilant when tasked with caring for the acutely ill toddler.

The following case demonstrates the importance of directed questioning and the need for maintenance of high suspicion for underlying occult pathology in the young pediatric population presenting with common complaints.

CASE PRESENTATION

A 19-month-old female presented to our pediatric emergency department (ED) with worsening constipation and abdominal pain. She was born near term (37 weeks 6 days gestation) and was small for gestational age at birth (1.59 percentile based on weight for age data from the Centers for Disease Control and Prevention [CDC] and the World Health Organization [WHO]). According to her parents and chart review, the patient had a long history of constipation (since the "first couple months of life"). It was documented that she did pass meconium within the first 48 hours of life. Regular primary pediatrician office visits documented a long-term history of constipation that previously had been well controlled with daily prune juice administration. Her recorded weights were at or below the 10th percentile for age (based on weight for age data from CDC and WHO) prior to the month leading up to presentation, consistently following her individual growth curve as would be expected. Her parents reported no changes in diet or suspicion for toxic/abnormal ingestions leading up to this presentation. Prior encounters clinicians in the week leading up to presentation noted decreased oral intake, increased fatigue, abdominal distension and pain, and lack of a recent bowel movement.

On arrival to the ED, the patient was notably fussy, dehydrated, and had a distended abdomen with hypoactive bowel sounds and a palpable stool burden. Vital signs throughout the clinical course are documented in the Table. She appeared thin and small for her age, which was corroborated on review of her growth chart (2nd percentile weight for age, down from the 10th percentile at a well child checkup 1 month prior). Abdominal x-ray was notable for a large stool burden with otherwise unremarkable findings. Chart review noted that she had lost approximately 1 kg over the prior month. Based on stool burden, exam, and history, a normal saline enema was administered without subsequent bowel movement over the next hour, after which a soap suds enema was administered, with modest stool production.

On repeat exam, the patient was fatigued with dry mucous membranes with persistent abdominal distension and tenderness, at which point a peripheral intravenous (IV) line was placed and a 1-time 20 ml/kg normal saline bolus was administered. Gastroenterology was consulted due to impressive stool burden and concern for weight loss in the setting of life-long constipation, warranting additional workup for failure to thrive. Repeat exam and vital sign review revealed a persistently dehydrated child, prompting an additional 20 ml/kg normal saline bolus. Given her minimal response to therapies, a comprehensive metabolic panel was run using blood initially obtained and held at the time of IV placement, to assess baseline electrolyte status in addition to general kidney and liver function prior to hospital admission. Laboratory results were notable for a severe

metabolic acidosis with a bicarbonate of < 8 mg/dL and an elevated anion gap of > 19 (using bicarbonate of 8), as well as blood glucose of 250 mg/dL.[1] The patient remained hemodynamically stable on maintenance IV fluids while further workup was done to evaluate the anion gap metabolic acidosis, including serum lactic acid, beta-hydroxybutyrate, and urinalysis. The urinalysis quickly revealed large ketones and glucosuria, consistent with DKA and associated new onset diabetes. Subsequently, the lactic acid was found to be normal and the beta-hydroxybutyrate level was elevated, also consistent with DKA. Because of the patient's severe metabolic acidosis and young age, she was admitted to the pediatric intensive care unit for further stabilization and management.

After diagnosis, the patient was placed on the "2 bag system" (simultaneous administration of an insulin drip and dextrose-containing fluid), after which her DKA quickly corrected within the next 24 hours, along with return to baseline neurologic status. She was subsequently transferred to the acute care floor for new onset diabetes parental teaching, as well as subcutaneous insulin administration training and titration prior to discharge. Close follow-up in the diabetes clinic was scheduled for later that week. Serum testing for type 1 diabetes-associated autoantibodies returned positive for GAD65 and highly sensitive insulin autoantibodies, confirming the diagnosis. She continues to follow-up with endocrinology and regularly attends her local primary pediatrician appointments with significant improvement in her weight trends (at age 35 months, weight was approximately 30th percentile for age consistently).

DISCUSSION

Unexpectedly, this patient who presented to the ED with complaints of constipation and abdominal pain was diagnosed with new onset type 1 diabetes after laboratory evaluation was obtained for dehydration and concern for failure to thrive. Given her young age, she was classified as extremely early onset type 1 diabetes, which carries a more severe prognosis.[3] It is postulated that individuals who develop type 1 diabetes at < 2 years of age have a more severe autoimmune phenotype, which leads to excessive beta cell destruction early in life.[3,14-16] Although extremely early onset diabetes is rare, the clinical pearls associated with such cases remain valuable across age groups for the pediatrician and emergency medicine provider, particularly for the patient presenting to the ED for acute on chronic abdominal pain with or without a history of constipation.[17-19]

The onset of constipation early in life, as in this case (around 4 to 6 months of age), requires additional investigation.[20-21] Our patient experienced constipation that had initially improved with over-the-counter therapies but worsened acutely leading up to presentation.

Constipation is a common childhood complaint that rarely has a known causative etiology, nor does every child warrant an extensive workup to determine one.[20-21] In this patient's case, her growth trends were consistently tracking along the 10th percentile or less for age, which is low but not necessarily pathologic if consistent for that individual patient.[22] The acute worsening of her baseline constipation prompted a medical encounter at which time she was appropriately referred to our ED. A combination of factors likely led to the false assumption that her symptoms all were linked to acute on chronic constipation. This point is evidenced by her notable down-trending growth curve percentiles ("falling off her growth curve") despite an intact appetite. Additionally, more directed discussions with the patient's parents after the diagnosis revealed the presence of polyuria and polyphagia. Although diabetes is a generally common diagnosis in the pediatric population, this patient's young age and her previously diagnosed constipation (although of unknown etiology) likely led to provider anchoring bias, affecting clinical judgement and decision-making pertaining to additional evaluation on subsequent presentations.[23]

Regardless of the etiology, there were additional clues making the astute clinician unable to write off her conglomeration of symptoms as secondary to solely constipation. The first of these key clues is weight loss and/or drop in growth percentiles. Consistently tracking in a low weight percentile can be normal but warrants frequent reassessment and monitoring.[22] Alternatively, weight loss in a young pediatric patient without explanation or with intact appetite is not normal, nor is constipation a sufficient explanation for it. A slew of gastrointestinal (GI) complaints/disorders are common in patients with type 1diabetes.[24] In a study of patients < 2 years old diagnosed with type 1 diabetes, 45% were noted to have weight loss prior to presentation, while about 10% reported constipation.[25] Although weight loss was reported among the majority of age groups at diagnosis, constipation was reported most in toddlers diagnosed at < 2 years of age.[25] Quinn et al found that parents were significantly less likely to report symptoms of hyperglycemia, such as polydipsia, polyuria, and polyphagia, in patients < 2 years old.[14] Although GI complaints are common in the emergency setting, we recommend quick review of the patient's growth curve to help guide the provider in terms of the true chronicity of the presenting condition as well as the severity of the issues described. Evaluation for the etiology of chronic constipation – especially in patients with symptom onset early in life coupled with marginal or no response to standard first-line medical therapies – is warranted as it can be associated with multiple additional health issues or be masking an occult systemic pathology.[18-21,24,26-28] The patient presenting with acute on chronic abdominal pain requires astute history gathering and examination with each presentation in order to ensure an underlying condition is not missed. Abdominal complaints – especially lower gastrointestinal complaints such as constipation, diarrhea, or an alternating pattern – can be a symptom of undiagnosed diabetes.[24]

The patient's altered mental status represented another diagnostic clue. This can be difficult to ascertain in a 19 month old

who is not feeling well, as there is often a high component of stranger anxiety in the hospital setting.[29] However, her transition from apprehensive of the medical team to sleeping uninterrupted despite their presence, was a notable derivation from baseline. With increased rates of DKA at diagnosis in younger patients, the risk of cerebral edema and, thus, neurologic status aberrations secondary to metabolic derangement also is increased.[8,10-13,30,31] This highlights the importance of serial exams and evaluation after each intervention. Serial exams in this patient appropriately cued the physicians to consider a broader differential and perform laboratory testing that led to the diagnosis.

Lastly, vital sign aberrations and examination findings out of proportion to the described clinical course or medico-social history warrant further evaluation, especially in the pediatric population where history gathering is often difficult. In the case presented here, the patient was significantly more dehydrated than would be expected based on history and context. This was evidenced by her minimal response to the initial fluid bolus and signs of hemoconcentration on lab evaluation. In a child with decreased oral intake but no emesis or diarrhea, one would not expect such profound dehydration as was demonstrated here. Seemingly small or insignificant hemodynamic changes are often the first manifestation of an underlying pathology at play.[32-34] Continued review—especially by adult emergency medicine providers—of normal age range standards is imperative, as is monitoring of hemodynamic trends in patients throughout their stay (ie, heart rate before and after fluid bolus).[35]

CONCLUSIONS

Extremely early onset type 1 diabetes is a rare diagnosis of a well-known pediatric disease that often presents with a vague constellation of symptoms. We present the case of a young child thought to have acute on chronic constipation who was subsequently found to be in DKA. Clinicians should remain vigilant when caring for this unique population to avoid anchoring bias and obtain appropriate work-up as to not miss this high-risk condition.

Funding/Support: None declared.

Financial Disclosures: None declared.

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