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CASE REPORT

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Ketoacidosis Onset of Diabetes on a Patient with Normal C-Peptide Value

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ABSTRACT

Background: *Diabetic ketoacidosis is an acute major life-threatening complication of diabetes, characterized by hyperglycemia, ketoacidosis and ketonuria, which can be life threatening if it is not promptly recognized and treated. This occurs mainly in patients with type 1 diabetes, but stressors like trauma and infection can increase the risk of ketoacidosis in other forms of diabetes such as type 2 diabetes. Type 2 diabetes mellitus is a complex metabolic disorder of heterogeneous etiology with behavioral, social, and environmental risk factors that unmask the effects of genetic susceptibility. Recent studies indicate an increasing prevalence of type 2 diabetes mellitus in children and adolescents around the world in all ethnicities. C-peptide is a useful and widely used method of assessing pancreatic beta cell function given his structure: part of proinsulin which is cleaved prior to co-secretion with insulin from pancreatic beta cells. This is used as a tool in the differentiation of type 1 diabetes from type 2 but also other types of diabetes.*

We present a 12-year-old previously healthy male who was hospitalized in our clinic for polydipsia, polyuria, weight loss and emesis, with symptom onset 10 days prior to admission. On the admission day, he presented to the emergency room for progressively increasing somnolence, apathy, decreased muscle tone and urinary incontinence. Physical examination was significant for grade I obesity [height 168 cm and weight 90 kg, yielding a body index mass (BMI) of 31.78 kg/m^2, percentile >97%], lethargy, slurred speech, high blood pressure (145/90 mmHg), tachycardia (145 beats per minute) and acanthosis nigricans. Considering his physical examination, laboratory tests and clinical evolution, he was diagnosed with type 2 diabetes mellitus complicated with hyperosmolar hyperglycemic state and diabetic ketoacidosis.

Diabetic ketoacidosis should be considered in the differential diagnosis of metabolic decompensation in all types of diabetes. Although type 2 diabetes mellitus seems to be still rare in childhood and adolescence, prevention and treatment of type 2 diabetes mellitus should become public awareness and public health intervention programs.

The particularity of this case was the unusual onset of diabetes mellitus type 2 in a male child with metabolic syndrome.

Keywords: children, type 1 diabetes, type 2 diabetes, C-peptide.

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INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute metabolic complication of diabetes mellitus that can be life threatening if not promptly recognized and treated (1). This acute major life-threatening complication of diabetes is characterized by hyperglycemia, ketoacidosis and ketonuria. The pathophysiology of DKA is characterized by absolute or relative insulin deficiency that inhibits the ability of glucose to enter cells for utilization as metabolic fuel. This insulin deficiency in concert with increased counter-regulatory hormone secretion and peripheral insulin resistance leads to hyperglycemia, ketosis, dehydration and electrolyte imbalance (2, 3). Diabetic ketoacidosis mainly occurs in patients with type 1 diabetes, but stressors like trauma and infection can increase the risk of DKA in other forms of diabetes that is why DKA is not uncommon in some patients with type 2 diabetes for example (4).

Type 1 diabetes results from the autoimmune destruction of β-cells in the pancreas and the subsequent lack of insulin (5). In the US, 30–46% of children are newly diagnosed with type 1 diabetes complicated at onset with this life-threatening complication called diabetic ketoacidosis (6). In 2014, the SEARCH for Diabetes in Youth (SEARCH) study reported that one in three US youth with type 1 diabetes is diagnosed with DKA and this proportion has not declined throughout the first decade of the 21st century (7). Presentation in DKA is thought to reflect more advanced pancreatic β-cell destruction during the preclinical evolution of the disease. Also, longer hospitalizations, higher insulin requirements, devastating immediate consequences such as increased mortality risk and a shorter remission period is associated with the presence of DKA at onset of type 1 diabetes (8-10). A study from Colorado, which was published in 2017, found a detrimental effect of DKA at diagnosis of type 1 diabetes in children on overall hemoglobin A_{1c} (HbA_{1c}) levels, an effect that was sustained for the following 15 years and was independent of socio-demographic factors (11).

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder of heterogeneous etiology with behavioral, social, and environmental risk factors that unmask the effects of genetic susceptibility (12). Although many years ago, in the last thirty years ago, type 2 diabetes mellitus has been thought to be a rare occurrence in children and adolescents, nowadays type 2 diabetes mellitus is emerging as a new clinical problem within pediatric practice. Recent studies indicate an increasing prevalence of T2DM in children and adolescents around the world in all ethnicities (13). In some regions of the US, T2DM is described as frequent as type 1 diabetes mellitus in adolescents (14). There is also a high increase in both the prevalence and degree of obesity in children and adolescents in many populations (15, 16). In our days, overweight is the most common health problem regarding children in both developed and developing countries (16). Although obesity is no longer increasing in the US and some countries in Europe (17, 18) the prevalence of T2DM has been increased threefold. This happens because of the degree of obesity in affected children and adolescents is increasing (18). In the development of T2DM in children puberty appears to play a major role (14). There is an increased resistance to the action of insulin during puberty that leads to hyperinsulinemia but after puberty, basal and stimulated insulin responses decline. Insulin resistance during puberty is discussed to be secondary to an increased growth hormone secretion (19). Taking by this information, there is no surprise that the peak age at presentation of T2DM in children overlaps with the usual age of mid-puberty (14, 20).

The diagnosis of T2DM with a mild form is made during a routine medical check-up by detection of hyperglycaemia or glycosuria in an asymptomatic patient (21). During routine physical examination, almost one third of patients are diagnosed by urine analysis (14, 21). When a child presents with polyuria, polydipsia and weight loss, there is a severe form and in very rare cases, T2DM manifests with a hyperglycaemic hyperosmolar coma. In these situations of polyuria, polydipsia and weight loss or hyperglycaemic hyperosmolar coma, the distinction from type 1 diabetes mellitus is not possible from the beginning and it lasts months to reach the correct diagnose. This happens when insulin requirements decline and a non-insulin-dependent course develops without dependence on insulin for survival.

C-peptide is a useful and widely used method of assessing pancreatic beta cell function given his structure: part of proinsulin which is cleaved prior

to co-secretion with insulin from pancreatic beta cells (22, 23). It is preferred to measure c-peptide and not insulin as a guide to beta cell function because the degradation rate of C-peptide in the body is slower than that of insulin (C-peptide has a half-life of 20–30 min while insulin has a half-life of just 3–5 min). This difference in the half-life time affords a more stable test window of fluctuating beta cell response (24). C-peptide is used as a tool in the differentiation of type 1 diabetes from type 2 diabetes but also MODY or LADA. There is evidence described that C-peptide can play a role in the diagnosis of latent autoimmune diabetes of adults (LADA), which can be misdiagnosed as T2DM (25-27). In this situation, the C-peptide value is significantly lower in LADA compared with T2DM (27). Maturity-onset diabetes of the young (MODY) a rare genetic form of diabetes, can be misdiagnosed as T1DM (28) that is why some researchers proposed C-peptide as a useful biomarker in the detection of MODY prior to genetic testing (29). ❑

CASE REPORT

We present a 12-year-old previously healthy male who was hospitalized in our clinic for polydipsia, polyuria, weight loss and emesis, with symptom onset 10 days prior to admission. Initial symptoms included polydipsia, polyuria and weight loss. On day 7 he presented multiple episodes of emesis for which he received symptomatic treatment at home. Three days later, on admission day, he presented to the emergency room for progressively increasing somnolence, apathy, decreased muscle tone and urinary incontinence. A very important detail to mention from the anamnesis was that his diet included weekly fast food and daily high sugar content beverages (such as 6–8 liters of soda *per* day).

Physical examination was significant for grade I obesity [height 168 cm and weight 90 kg, yielding a body index mass (BMI) of 31.78 kg/m^2, percentile >97%], lethargy (Glasgow coma scale GCS – 10), slurred speech, high blood pressure (145/90 mm Hg), tachycardia (145 beats per minute) and acanthosis nigricans.

At admission, initial laboratory tests revealed a very high serum blood glucose level (2 466 mg/dL), with a hemoglobin A1c of 12.27%; the pH was 7.257 (reference range 7.35-7.45), PCO_2 54 mm, measured bicarbonate 24.6 mmol/L and base deficit of -3.5 mmol/L, with an osmolarity of 262 mOsm/Kg (reference range 275-295 mosm/kg). Also, electrolyte values showed hyponatremia – 131 mmol/L (reference range 135-145 mmol/L), hypocalcemia 6.5 mg/dL (reference range 8.4-10.2 mg/dL); urine analysis showed glycosuria (1 000 mg/dL) with minimal urinary ketones (5 mg/dL); lipidic profile: total cholesterol 108 mg/dL (reference range 0-200 mg/dL), low-density lipoprotein cholesterol (LDL) cholesterol 60 mg/dL (reference range 0-100 mg/dL),very low-density lipoprotein cholesterol VLDL cholesterol – 64 mg/dL (reference range 0-30 mg/dL), high-density lipoprotein (HDL) cholesterol 18 mg/dL (reference range > 40 mg/dL), triglyceride 319 mg/dL (reference range 0-150 mg/dL); blood urea nitrogen (BUN) 36 mg/dL (reference range 0-18 mg/dL), creatinine 0.79 mg/dl (reference range 0-0.79 mg/dL); Free tyroxine (FT4) 16.4 pmol/L (reference range 12.6-21 pmol/L) and thyroid-stimulating hormone (TSH) 1,2 micro Ui/mL (reference range: 0,51-4,30 microUi/mL); C-reactive protein 3 mg/dL (reference range of 0-5 mg/dL), negative procalcitonin and negative blood culture at seven days. It should be mentioned that C-peptide was 1.25 ng/mL (reference range 1.1-4.4 ng/mL), glutamic acid decarboxylase antibody, insulin autoantibody and islet cell antibodies were within reference range, demonstrating a negative workup for type 1 diabetes mellitus. A chest X-ray was unremarkable and abdominal ultrasound showed a slight hepatomegaly (prerenal diameter of the right hepatic lobe measured 168 mm) with a homogeneous, hyperechoic image of the liver.

The patient was admitted to the intensive care unit and received hydroelectrolytic rebalancing with intravenous normal saline during the first hours, followed by continuous insulin infusion starting at a rate of 0.1 UI/kg/h. After cardiologic examination for high blood pressure (highest value 160/90 mm Hg), treatment with anti-hypertensive agents – calcium channel blockers (Amlodipine) – was started. After 10 hours of fluid resuscitation, glucose levels decreased to 1 028 mg/dL, with elevated sodium (151 mmol/L) and developed hyperglycemic hyperosmolar state: pH 7.366, HCO_3 21.2 mmol/L, plasma osmolality 307 mOsm. After 24 hours, his mental status improved continuously and 48 hours post-presentation he responded to commands and was oriented to place and person. Serum glucose gradually

decreased to 551 mg/dL, but serum creatinine and gradually increased to 1.78 mg/dL. By the fourth day, the patient was in stable condition and was transferred to the pediatric ward. He was transitioned from intravenous to subcutaneous insulin and was permitted oral intake with a regular diet and blood glucose monitoring.

He was diagnosed with metabolic syndrome with type 2 diabetes mellitus complicated with HHS and DKA. Three months after discharge, physical exam was significant for grade I obesity [height 169 cm and weight 89 kg, body index mass (BMI) of 31.16 kg/m^2, percentile >97%], but his test improved as follows: fasting blood glucose 112 mg/dL, hemoglobin A_{1c} 5.8%, and c-peptide 6.04 ng/mL. ❑

DISCUSSION

DKA and HHS represent two extremes in the spectrum of complications of diabetes mellitus and are characterized by hyperglycemia and absolute or relative insulinopenia (30). Clinically, they differ by the severity of dehydration, ketosis and metabolic acidosis. In DKA, insulin deficiency and ketoacidosis are the prominent features of the clinical presentation and insulin therapy is the cornerstone of therapy. The incidence of HHS in children is lower than DKA as it is usually associated with type 2 diabetes. Recognising HHS as a distinctive entity is sometimes very hard and this can mislead doctors to treat HHS with DKA protocols. In HHS hyperglycemia, osmotic diuresis and dehydration are the prominent features with emphasis on fluid replacement as a first step of treatment. Insufficient replacement of the depleted intravascular volume may increase the mortality rate, as vascular collapse, thrombosis and ischemia have a greater risk to appear.

In children with mixed HHS and DKA, the initial treatment should take into consideration that, in DKA, fluid therapy is intended to correct acidosis and dehydration, but correcting the insulin deficit is the most important; meanwhile, in HHS, fluid therapy should be carefully administered to avoid rapid changes in serum osmolality. Also, you need to take care during treatment about the potential complications that could arise such as electrolyte imbalance, cerebral edema, ischemic injury – acute renal failure, hyperamylasemia or rhabdomyolysis.

Our patient had an unusual onset of diabetes mellitus type 2 – mixed HHS and DKA. Blood glucose >600 mf/dL, bicarbonate >15 mEq/L, trace of urine ketone and hypernatremia met the criteria for HHS and arterial pH <7.3 with an osmolality under 320 mosm/kg from the first hours indicated DKA. Obesity and the intake of carbonated sugar enriched drinks on a daily basis were factors that accelerated the hyperglycemic state. ❑

CONCLUSION

Diabetic ketoacidosis is a serious acute metabolic complication of diabetes that can affect people with types of diabetes other than type 1. This should be considered in the differential diagnosis of metabolic decompensation in all types of diabetes.

Although type 2 diabetes mellitus seems to be still rare in childhood and adolescence, because recent reports indicate an increasing prevalence around the world probably due to an increasing prevalence of obesity in children and adolescent, prevention and treatment of type 2 diabetes mellitus should become public awareness and one of the prime targets of public health intervention programs.

The particularity of this case was the unusual onset of diabetes mellitus type 2 in a male child with metabolic syndrome. ❑

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References

1. **Fayfman M, Pasquel FJ, Umpierrez GE.** Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. Medical Clinics of North America 2017, vol. 10.
2. **Laffel L.** Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Res Rev* 1999;6:412-426.
3. **Osama Hamdy.** What is diabetic ketoacidosis (DKA)? [Internet]. *Medscape*. 2021. Available from: https://emedicine.medscape.com/article/118361-overview.
4. **Barski L, Nevzorov R, Harman-Boehm I,**

et al. Comparison of diabetic ketoacidosis in patients with type-1 and type-2 diabetes mellitus.
Am J Med Sci 2013;3:326-330.

5. **Atkinson MA, Bluestone JA, Eisenbarth GS, et al.** How does type 1 diabetes develop? The notion of homicide or β-cell suicide revisited.
Diabetes 2011;5 1370-1379.
6. **Rewers A, Dong F, Slover RH, et al.** Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998-2012.
JAMA 2015;15:1570-1572.
7. **Dabelea D, Rewers A, Stafford JM, et al.** Trends in the prevalence of ketoacidosis at diabetes diagnosis: The search for diabetes in youth study.
Pediatrics 2014;4:e938-e945
8. **Dunger DB, Sperling MA, Acerini CL, et al.** European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents.
Pediatrics 2004;2:e133-e140.
9. **Bowden SA, Duck MM, Hoffman RP.** Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: Diabetic ketoacidosis is an important risk factor.
Pediatr Diabetes 2008;3 Pt 1:197-201.
10. **Böber E, Dündar B, Büyükgebiz A.** Partial remission phase and metabolic control in type 1 diabetes mellitus in children and adolescents.
J Pediatr Endocrinol Metab 2001;4:435-441.
11. **Duca LM, Wang B, Rewers M, Rewers A.** Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control.
Diabetes Care 2017;9:1249-1255.
12. **Kiess W, Böttner A, Raile K, et al.** Type 2 diabetes mellitus in children and adolescents: A review from a European perspective. In:
Hormone Research 2003.
13. **Arslanian S.** Type 2 diabetes in children: Clinical aspects and risk factors. In:
Hormone Research 2002;57(Suppl 1):19-28..
14. **Arslanian SA.** Type 2 diabetes mellitus in children: Pathophysiology and risk factors. In:
Journal of Pediatric Endocrinology and Metabolism 2000;Suppl 6:1385-1394..
15. **Lobstein T, Frelut ML.** Prevalence of overweight among children in Europe.
Obesity Reviews 2003;4:195-200.
16. **The Lancet**. Childhood obesity: affecting choices.
The Lancet 2010;375:611.
17. **Moss A, Klenk J, Simon K, et al.** Declining prevalence rates for overweight and obesity in German children starting school.
Eur J Pediatr 2012;2:289-299..
18. **May AL, Kuklina E V, Yoon PW.** Prevalence of cardiovascular disease risk factors among US Adolescents, 1999-2008.
Pediatrics 2012;6:1035-1041.
19. **Pinhas-Hamiel O, Lerner-Geva L, Copperman NM, Jacobson MS.** Lipid and insulin levels in obese children: Changes with age and puberty.
Obesity 2007;15:2825-2831.
20. **Reinehr T.** Clinical presentation of type 2 diabetes mellitus in children and adolescents.
Int J Obes 2005;Suppl 2:S105-S110.
21. **Rosenbloom AL, Silverstein JH, Amemiya S, et al.** Type 2 diabetes mellitus in the child and adolescent.
Pediatr Diabetes 2008;5:512-526.
22. **Jones AG, Hattersley AT.** The clinical utility of C-peptide measurement in the care of patients with diabetes.
Diabetic Medicine 2013;7:803-817.
23. **Kulkarni CM, Patil S.** Urinary C-peptide and urine C-peptide/creatinine ratio (UCPCR) are possible predictors of endogenous insulin secretion in T2DM subjects - A randomized study.
Int J Pharma Bio Sci 2016;4:443-446.
24. **Steiner DF, Cunningham D, Spigelman L, Aten B.** Insulin biosynthesis: Evidence for a precursor.
Science 1967;3789:697-700.
25. **Bell DSH, Ovalle F.** The role of C-peptide levels in screening for latent autoimmune diabetes in adults.
Am J Ther 2004;4:308-311.
26. **Arikan E, Sabuncu T, Ozer EM, Hatemi H.** The clinical characteristics of latent autoimmune diabetes in adults and its relation with chronic complications in metabolically poor controlled Turkish patients with Type 2 diabetes mellitus.
J Diabetes Complications 2005;5:254-258.
27. **Sujesh Kumar N, Subhakumari KN.** Role of anti-GAD, anti-IA2 antibodies and C-peptide in differentiating latent autoimmune diabetes in adults from type 2 diabetes mellitus.
Int J Diabetes Dev Countries 2016;3:313-319.
28. **Hattersley A, Bruining J, Shield J, et al.** ISPAD Clinical Practice Consensus Guidelines 2006-2007. The diagnosis and management of monogenic diabetes in children.
Pediatr Diabetes 2006;6:352-360.
29. **Besser REJ, Shepherd MH, McDonald TJ, et al.** Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-{alpha}/hepatocyte nuclear factor 4-{alpha} maturity-onset diabetes of the young from long-duration type 1 diabetes.
Diabetes Care 2011;2:286-291.
30. **Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA.** Hyperglycemic crises in adult patients with diabetes: A consensus statement from the American Diabetes Association. In:
Diabetes Care 2006;12:2739-2748.