The Turkish Journal of Pediatrics 2018; 60: 201-205
DOI: 10.24953/turkjped.2018.02.015

Case Report

Low hemoglobin A1c levels in a patient with diabetic ketoacidosis: Fulminant type 1 diabetes mellitus

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Received: 10th May 2016, Revised: 9th December 2016, 15th January 2018, Accepted: 18th January 2018

SUMMARY: Keskin M, Savaş-Erdeve Ş, Çetinkaya S, Aycan Z. Low hemoglobin A1c levels in a patient with diabetic ketoacidosis: Fulminant type 1 diabetes mellitus. Turk J Pediatr 2018; 60: 201-205.

Fulminant type 1 diabetes mellitus (FT1DM) is a clinical condition that is characterized by remarkably rapid and complete pancreatic β-cell destruction, rapid onset of hyperglycemic symptoms followed by ketoacidosis. In most cases this process takes a few days. Although rare, there have been clinical manifestations with a prolonged progress that lasts longer than one week.

This study focused on the case of a 35-monthold boy who was referred to our clinic with the diagnosis of diabetic ketoacidosis, and later had a modest elevation in hemoglobin A1c (HbA1c) levels (6.7 %) incompatible with his significantly elevated blood glucose levels. The autoantibodies against pancreatic β-cells were negative. On the basis of these above mentioned findings, our patient was then diagnosed with fulminant type 1 diabetes mellitus.

If patients with diabetic ketoacidosis have no elevation in HbA1c levels, they should be assessed for possible clinical factors that can lead to lower detectable levels of HbA1c. Furthermore, FT1DM which is characterized by very rapid and potentially fatal progression should be considered as a differential diagnosis in these patients.

Key words: childhood, diabetic ketoacidosis, insulin dependent diabetes mellitus.

Fulminant type 1 diabetes mellitus (FT1DM) is a subtype of type 1 diabetes mellitus (T1DM) reported in 2000 by Imagawa et al[1]. FT1DM develops as a result of a very rapid and almost complete pancreatic ß-cell destruction. Symptoms related to hyperglycemia include polydipsia, polyuria and weight loss and tend to occur in less than a week. Symptoms tend to develop within a mean of 4.4±3.1 days.[2] FT1DM has previously been shown to account for approximately 20% of Japanese patients diagnosed with T1DM.[3] In South Korea, the prevalence of FT1DM among patients with a novel diagnosis of T1DM has been found to be 7.1%, while rates are much higher for patients with adult-onset diabetes (30.4%).[4] The etiology of FT1DM has not been fully understood yet, but hereditary factors such as specific human leukocyte antigens (HLA) class, and environmental factors, such as viral infections, are thought to play crucial roles in the progress of pancreatic ß-cell dysfunction.[2,5]

FT1DM is characterized by onset of diabetic ketoacidosis within a short period mostly less than 7 days, normal or near-normal hemoglobin A1c (HbA1c) levels at onset of the disease, together with complete β-cell destruction.[2] The disease is related to increased serum pancreatic enzyme levels, low C-peptide levels and negative detection of pancreatic β-cell auto-antibodies. The presence of the above mentioned characteristics strongly indicates FT1DM diagnosis. When the diagnosis of FT1DM is established or when such a diagnosis is considered, similar to other subtypes of type 1 diabetes mellitus, an immediate treatment is crucial.[2,6]

In summary, our patient was a 35-month old boy diagnosed with FT1DM. Presenting complaints, laboratory test results and follow-up assessments were discussed to provide a deeper understanding regarding the clinical condition outlined.

Case Report

A 35 months old male patient was admitted to our hospital's emergency department with the complaint of dyspnea. Clinical history revealed that the patient was suffering from mild fever, rhinitis, and cough for four days prior to emergency admission. Additionally, caregivers reported that polydipsia and polyuria started two days ago, whereas dyspnea started only few hours prior to his hospital admission. The patient was lethargic and had second-degree dehydration in addition to acidotic breathing. Laboratory test results were presented in Table I.

Considering the clinical history, physical examination and laboratory results, the patient was diagnosed with diabetic ketoacidosis. Then, fluid replacement therapy and crystallized insulin infusion, which was later replaced by intensive insulin therapy were initiated. The clinical profile of the patient was compatible with diabetic ketoacidosis, including elevated serum glucose levels. However, we observed a slight elevation in HbA1c levels which is normally expected to significantly increase in diabetic ketoacidosis. Following this assessment we went on to investigate secondary medical conditions that might have led to the clinical condition of our patient (including malaria,

Table I. Laboratory Data of Patient at the Time of Admission and Follow-up.

Hematology
WBC 7.6 $\times 10^3/\mu$l (5.1-15.5)
RBC 4.83$\times 10^6$ /μl (3.3-5.4)
Hb 12.6 g/dl (9.8-13.4)
Ht 37.4% (28.3-40)
Plt 327 $\times 10^3/\mu$l (159-353)
Peripheral smear: Normochromic normocytic morphology

Biochemistry
Glucose (mg/dl): 547 (70-110)
Sodium (mEq/l):132 (135-143)
Potassium (mEq/l): 4.6 (3.1-5.5)
BUN (mg/dl): 17 (0-23)
Creatinine (mg/dl): 0.77 (0.3-1.2)
Uric acid (mg/dl): 9.1 mg/dl (<6.1)
ALT (U/L): 32 (0-39)
AST (U/L): 18 (<48)
On admission: HbA1c (%): 6.7 (4.6-6.2)
Fructosamine (umol/L):342 (<285)
Insulin (μIU/ml) : 0.27
On admission C-peptide (ng/ml): 0.07 (0.9-7.1)
12.th months C-peptide (ng/ml): 0.06 (0.9-7.1)
Iron (μg/dl) : 44 (36-184)
Vitamin B_{12} (pg/ml): 317 (200-1220)
Folic acid (ng/ml): 11.2 (3-17)
Ferritin (ng/ml): 32.7 (6-24)

Amylase (U/L) : 142 (25-125)
Lipase (U/L): 94 (8-78)
Serum ketone: ++

Metabolic Analysis
Tandem MS: Normal
Plasma and urine amino acids: Normal
Urine organic acid analysis: Normal

Blood gas analyses
PH: 6.99
PO_2 (mmHg):140.4
PCO_2 (mmHg):8.5
HCO_3(mmol/L): 6.1
BE(mmol/L):-26.5

Autoantibodies	On Admission	At 12th month
Anti-GAD ab (IU/ml):	7.2	4.3 (<10)
Anti-islet ab:	(-)	(-)
Anti-insulin Ab (%BO):	0.76	0.42 (0-7)

Viral antibodies
CMV Ig G: (-)
EBV Ig G: (-)
Parvovirus Ig G: (-)
HSV Ig G: (-)

Urinalyses
Specific gravity: 1035 (1006-1030)
Glucose: 4+
Protein: (-)
Ketone bodies: 3+
White blood cells: (-)

chronic anemia, large quantities of blood loss, hemolysis, uremia, pregnancy, smoking and various infections) (7). Laboratory results were presented in Table I. Despite performing a detailed analysis, we failed to identify a significant secondary cause. We can speculate that the duration between the presenting complaints and establishment of diabetic ketoacidosis diagnosis was approximately two days, which was shorter than usual. We also identified significantly low levels of C-peptide together with slight elevation in pancreatic enzymes in the absence of pancreatic β-cell autoantibodies. Collectively, we can state that these findings have led us to the diagnosis of FT1DM.

The patient has been under our medical monitoring for two years, and currently, 0.5 U/kg insulin per day is administered. Insulin doses and HbA1c levels were presented in Table II. Informed consent form was taken from parents.

Discussion

Fulminant type 1 diabetes mellitus (FT1DM) is a clinical condition in which β-cell destruction results with rapid development of hyperglycemia as well as ketoacidosis. Symptoms related to hyperglycemia develop in less than 7 days with a mean of 4.4±3.1 days.[2] Actually, a full progression in our case developed in about two days. The fast progression of the disease is not seen in patients with autoimmune diabetes mellitus which is characterized by slow progression.[2,5-6] Patients with autoimmune diabetes are known to present symptoms like polyuria, polydipsia and weight loss within an average of 36.4±25.1 days.[2]

In general, FT1DM progresses with very high plasma glucose levels while HbA1c levels show either a normal or a mild increase. However, when patients have low HbA1c levels as the patient we presented, further investigation is required in order to better understand possible contributing factors that may influence serum HbA1c levels before making a definite diagnosis of FT1DM. HbA1c levels may be altered by factors other than glycemic conditions. In particular, factors that affect erythrocyte turnover and hemoglobinopathy (such as malaria, chronic anemia, large quantities of blood loss, hemolysis, uremia, pregnancy, smoking, and various infections) can decrease HbA1c levels.[7] Patients with hemolytic anemia have lower HbA1c levels, while patients with iron deficiency anemia tend to have higher levels. Lower HbA1c levels can also be due to renal anemia in chronic kidney failure and chronic liver diseases in which there is hypersplenism that results in declines in erythrocyte half-life.[8] Our patient had normal kidney and liver functions and no anemia. Iron, vitamin B12, folic acid and ferritin levels were all normal and erythrocyte morphology was normal. The patient had no blood loss in his medical history. Viral serology was negative. A mild increase in both fructosamine and HbA1c levels were observed. HbA1c levels in discordance with elevated blood glucose levels were indicative of a FT1DM diagnosis.

Even though FT1DM can be observed in every age group, it is most frequently seen in ages over 20.[5] The youngest case ever presented was a one-year-old patient.[2] In a study in which 161 cases with FT1DM were presented, 1.9% of the patients were younger than 9 years. Our patient was diagnosed with fulminant type 1 diabetes at the age of 2 years and 11

Table II. The Average Insulin Doses and HbA1c Levels During Clinical Follow-up.

Follow-up	Average insulin dose (U/kg/day)	HbA1c (%)
Third month	0.78	6.3
Sixth month	0.78	6.9
Ninth month	0.76	6.6
One year	0.63	7.2
One year and third month	0.57	7.2
One year and sixth month	0.54	6.2
One year and ninth month	0.5	6.8
Two years	0.5	8.7

months. A major problem of diagnosing such a young patient is the difficulty of the young age children to explain their own complaints. If clinicians do not pay attention, this would result in missing the complaints of this age group. In our case, polydipsia and polyuria were noticed by the patient's family and were very informative symptoms in aiding our subsequent diagnosis.

Anti-islet, anti-insulin and anti-GAD antibodies are frequently found to be negative in FT1DM patients, and these auto-antibodies were also negative in our case.[9] Our patient was under medical monitoring for more than two years, and a re-assessment for autoantibody levels at the end of this period still revealed negative results. Another finding typical of this form of T1DM is significantly low levels of C-peptide.[9] Our patient had a low C-peptide level of approximately 0.07 ng/ml, while the plasma glucose level was elevated to a value of 557 mg/dl. This, indeed, was a strong indication of complete β-cell destruction, which would occur during the rapid progression of the disease. Also, follow-up examinations for C-peptide levels still showed low values (Table I). In addition to the outlined indications, our patient also had elevated levels of pancreatic enzymes on admission, which is a common observation among other patients with FT1DM. $CD3^+$ T cell-predominant infiltration of the exocrine pancreas was observed during the diagnosis of fulminant type 1 diabetes. Additionally, elevations in serum pancreatic amylase, lipase, elastase-1 and phospholipase levels were consistent with the histology of fulminant type 1 diabetes.[1] Pancreatic swelling is rarely reported in computed tomography or ultrasonography, and elevated serum pancreatic enzyme levels as well as pancreatic swelling tend to disappear during the treatment of diabetic ketoacidosis.[9] For instance, in the study of Cho and colleagues, 99 patients newly diagnosed with type 1 diabetes were included and seven (7.1%) of these patients fulfilled the criteria of fulminant type 1 diabetes.[4] Of the patients, aged 18 years or older at onset, 30.4% had a fulminant type 1 diabetes, and no patient with an age of onset younger than 18 years was diagnosed with the disorder. Additionally, authors determined elevated levels of exocrine pancreatic enzymes, such as amylase and lipase, in five patients. Four of these patients were later reported to undergo abdominal imaging tests (computed tomography or sonography), but authors did not report any evidence of pancreatitis.[4] In another study, Imagawa and colleagues enrolled 161 adults with fulminant type I diabetes and identified elevated levels of amylase enzymes in 74 patients and lipase enzymes in 50 patients, normal amylase levels in 54 patients and normal lipase levels in 9 patients.[10] These levels were found to be significantly higher compared to that of autoimmune type 1 diabetes.[10] Amylase and lipase enzyme levels were evaluated with respect to their laboratory reference values. The lipase level reference interval was taken to be 22-51 IU/L in Cho et al.[4], and they reported cases with elevated levels such as 285, 124, 148 and even, 942IU/L.The same researchers accepted reference interval values for amylase enzyme to be 60-180 IU/L, and reported elevated levels as 233 and 312 IU/L. [4] The patient we reported had an amylase level of 142 IU/L (25 - 142) and a lipase level of 94 IU/L (8 - 78).

Class 2 HLA are thought to have important roles in the etiology of fulminant type 1 diabetes. However, the factors that lead to β-cell destruction are still far from being definitively outlined. Several viral agents are thought to be possibly involved in the etiology of the condition, and it is especially informative to consider prior history of viral infections in many cases with FT1DM.[2] Previous studies, for instance, reported relationships between FT1DM and Coxsackie virus type A2 as well as human herpes virus type 6.[11,12] It may be noteworthy that our patient also reported symptoms indicative of a viral infection including fever, coughing episodes and rhinitis prior to admission. We should also note that even though the rate of comorbid viral infections with type 1 diabetes are reported to occur in 26.9% of cases, this percentage rises dramatically to 71.7% in patients with FT1DM.[2]

In cases when diabetic ketoacidosis develops rapidly concurrent with normal or slightly increased HbA1c levels, clinicians are advised to consider FT1DM in differential diagnosis. Prior to FT1DM diagnosis, possible contributing factors potentially affecting erythrocyte turn-over leading to lower HbA1c levels should to be assessed carefully.

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