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Case Report

Ketosis-prone Diabetes as a Presentation of New-onset Diabetes in a Patient With Spinal Muscular Atrophy Type III

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Abstract

Spinal muscular atrophy (SMA) is a genetic motor neuron disease that leads to reduced muscle mass and muscle weakness. Recent studies demonstrated that metabolic complications could develop as emerging complications among patients with SMA and long-term follow-up. Sarcopenia together with aberrant glucose and fatty acid metabolism can predispose those with SMA to develop diabetes and diabetic ketoacidosis. Here, we present a patient with SMA type III who presented with ketosis-prone diabetes as an initial presentation of diabetes. Pancreatic autoantibodies (anti-GAD and anti-IA2) and a monogenic diabetes genes panel revealed negative results. A polygenic risk score for type 2 diabetes revealed a low genetic risk for type 2 diabetes. After resolution of diabetic ketoacidosis, insulin therapy was successfully discontinued within 1 month after discharge and the patient has been treated with metformin in combination with thiazolidinedione. The possibility of metabolic abnormalities in patients with SMA should be considered among patients who live well into adulthood. Sarcopenia together with alterations in fatty acid and ketone metabolism could lead to ketosis-prone diabetes as an initial presentation of diabetes among patients with SMA.

Key Words: ketosis-prone diabetes, spinal muscular atrophy, type III, diabetic ketoacidosis, new-onset

Abbreviations: anti-IA2, anti-protein tyrosine phosphatase; DKA, diabetic ketoacidosis; KPD, ketosis-prone diabetes; SMA, spinal muscular atrophy; SMN1, survival of motor neuron 1; T2D, type 2 diabetes.

Introduction

Spinal muscular atrophy (SMA) is a rare monogenic lower motor neuron disease (estimated incidence of 1 in 6000-10 000 live births) and is caused by mutations in the survival of motor neuron 1 (*SMN1*) gene leading to degeneration of lower motor neurons with consecutive progressive muscle wasting [1]. The age of onset and the severity of SMA correlates with variations in the *SMN2* gene, which is adjacent to the *SMN1* gene [2]. The phenotypic features of SMA type III, which is the milder form of SMA, typically manifests after 18 months of age and can also develop later into early adolescence. Individuals with SMA type III are able to walk but may experience progressive muscle weakness later in life. Progression of SMA type III is slow and life expectancy is typically normal [3]. It is now apparent that various metabolic and endocrine abnormalities have been described in these patients from reduced muscle mass, abnormal glucose, and fatty acid metabolism [4, 5]. Patients with SMA are also prone to developing ketoacidosis from increased ketone production in times of stress [6]. Metabolic alterations in patients with SMA and animal models of the disease have been increasingly studied in the past decade [6-10].

Diabetic ketoacidosis (DKA) in adult patients with SMA had been reported in previous cases among patient with SMA type II [11, 12]. Here, we present an adult patient with SMA type III who presented with ketosis-prone diabetes (KPD) as an initial presentation of diabetes. KPD is a heterogeneous disease in terms of age at onset, residual β-cell function at the time of diagnosis, pancreatic autoantibodies status, and prognosis of insulin withdrawal rate [13, 14]. Our present case could be withdrawn from insulin treatment successfully at only 1 month after admission for DKA.

Case Presentation

A 27-year-old Thai man with a history of genetically confirmed SMA type III and no history of diabetes presented with polyuria and had lost 12 kg within 3 months (baseline body mass index at 25.0 kg/m^2). He denied fever, nausea, abdominal pain, shortness of breath, or worsening neurologic symptoms. The patient's medical history consisted of a normal term delivery with an appropriate gestational age weight after an uncomplicated pregnancy. At the age of 17 years, he developed proximal muscle weakness and was diagnosed with genetically confirmed SMA type III (homozygous deletion of exon 7 and 8 in the *SMN1* gene). His motor capabilities deteriorated slightly during adolescence but he could walk independently with limited physical activity. The latest annual medical checkup at the age of 22 years revealed normal fasting plasma glucose. His family history of diabetes included his father and his grandparents, as shown in Fig. 1. He was not taking any

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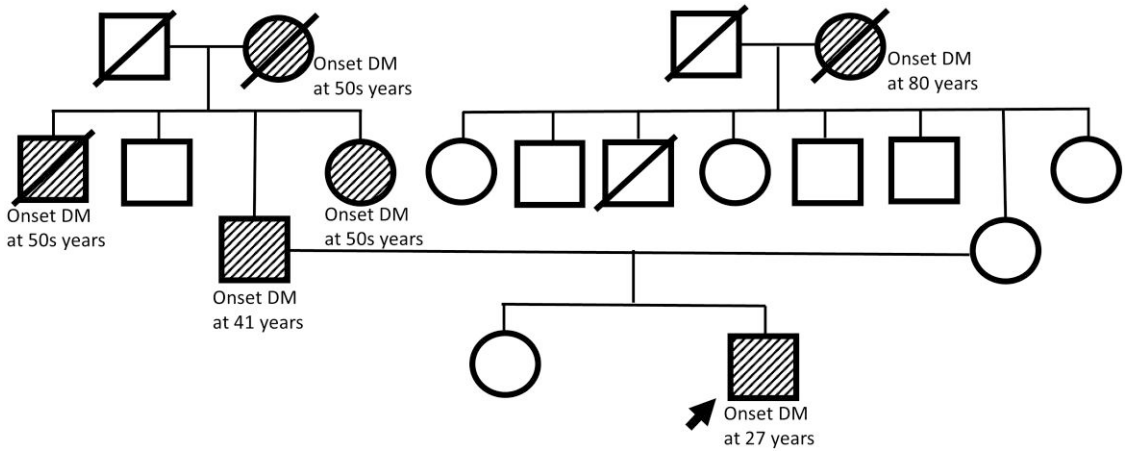

Figure 1. A family pedigree of this patient. Gray indicates the presence of diabetes mellitus.

medications and had no history of tobacco, alcohol, or illicit drug abuse. The patient also denied consuming a large amount of carbohydrates in the form of soft drinks recently. Physical examination at presentation revealed a fully pubertal young man with no dysmorphic face, dry mucous membranes, height of 171 cm, weight of 61 kg, and a body mass index of 20.9 kg/m^2. His body habitus revealed abnormal fat accumulation resulting in subcutaneous fat loss in upper arms and atrophy of the thigh muscles contrasting to hypertrophy of the calf muscles as shown in Fig. 2. His neurological examination showed normal cognition and cranial nerve function. Motor examination revealed normal tone, atrophy of shoulder, triceps, and hip girdle muscles, and moderate proximal muscle weakness in all 4 limbs, which was more prominent in the lower limbs. There was no tremor and no abnormal movement. His reflexes were absent. Sensation was intact. No acanthosis nigricans was present in the posterior neck or axilla.

Diagnostic Assessment

The initial laboratory evaluation revealed a fasting plasma glucose 403 mg/dL (SI: 22.4 mmol/L), glycated hemoglobin 12.0% (SI: 108 mmol/mol), ketonemia (β-hydroxybutyrate) at 3.1 mmol/L (32.3 mg/dL) (reference range, <0.6 mmol/L; <6.2 mg/dL), and venous pH 7.29. A basic metabolic panel showed a sodium level of 135 mEq/L (SI: 135 mmol/L) (reference range, 135-145 mEq/L [SI: 135-145 mmol/L]), potassium 4.7 mEq/L (SI: 4.7 mmol/L) (reference range, 3.5-5.0 mEq/L [SI: 3.5-5.0 mmol/L]), chloride 93 mEq/L (SI: 93 mmol/L) (reference range, 98-107 mEq/L [SI: 98-107 mmol/L]), serum bicarbonate 22 mEq/L (SI: 22 mmol/L) (reference range, 24-28 mEq/L [SI: 24-28 mmol/L]), anion gap 16 mEq/L (SI: 16 mmol/L) (reference range, <12 mEq/L [SI: <12 mmol/L]), creatinine 0.4 mg/dL (SI: 35.4 μmol/L) (reference range, 0.8-1.0 mg/dL [SI: 70.7-88.4 μmol/L]), plasma total cholesterol level of 209 mg/dL (SI: 5.4 mmol/L) (reference range, <200 mg/dL [SI: <5.2 mmol/L]), plasma triglyceride level of 113 mg/dL (SI: 2.9 mmol/L) (reference range, <150 mg/dL [SI: <3.9 mmol/L]), high-density lipoprotein cholesterol level of 38 mg/dL (SI: 1.0 mmol/L) (reference range, >45 mg/dL [SI: >1.2 mmol/L]), low-density lipoprotein cholesterol level of 164 mg/dL (SI: 4.3 mmol/L) (reference range, <130 mg/dL [SI: <3.4 mmol/L]), serum albumin 4.0 g/dL (SI: 40 g/L) (reference range, 3.5-5.2 g/dL [SI: 35-52 g/L]), serum aspartate aminotransferase 17 U/L (reference range, 0-40 U/L), serum alanine aminotransferase 25 U/L (reference range, 0-41 U/L), and serum alkaline phosphatase 86 U/L (reference range, 40-129 U/L). Calculated plasma osmolarity was 296 mOsm/L (SI: 296 mmol/L). Abdominal ultrasonography demonstrated a normal size of liver with slightly fatty infiltration and no abdominal mass.

Pancreatic autoantibodies (anti-GAD and anti-IA2) revealed negative results. Body composition measurement (bioimpedance analysis) showed excess fat percentage of 31.3% (normal range 10%-20%) and severe sarcopenia (skeletal muscle index = 5.7 kg/m^2, normal ≥7.0 kg/m^2).

Treatment

The patient was started on intravenous fluid and insulin infusion to treat DKA. He felt symptomatically better and out of DKA at 8 hours after admission. After resolution of DKA, basal bolus insulin regimen was given at a total daily dose of 36 units per day (0.6 units/kg/day).

Outcome and Follow-up

A random nonfasting plasma C-peptide after resolution of DKA for 1 week revealed residual β-cell function (plasma C-peptide 0.8 ng/mL; SI: 0.2 nmol/L) (reference range, 0.9-1.8 ng/mL; SI: 0.3-0.6 nmol/L). Insulin therapy was successfully discontinued within 4 weeks after discharge and he has since been treated with oral metformin in combination with thiazolidinedione. Monogenic diabetes genes panel revealed negative results. A validated polygenic risk score for type 2 diabetes (T2D), which was composed of 254 single-nucleotide polymorphisms to predict an individual's risk of developing the disease revealed a low genetic risk for T2D [15].

At 1 month after insulin discontinuation, a mixed meal stimulation test revealed preserved β-cell function (fasting plasma C-peptide at 1.2 ng/mL [SI: 0.4 nmol/L] and stimulated C-peptide at 6.2 ng/mL [SI: 2.1 nmol/L]). Homeostatic Model Assessment for Insulin Resistance index was normal (1.5; normal <1.6). At the last follow-up (5 months after DKA), the patient's diabetes has been well-controlled (glycated hemoglobin 6.4%) and his weight increased to 70 kg. No diabetes complications were detected. The patient was advised to maintain his body weight together with regular follow-ups for further SMA-related conditions.

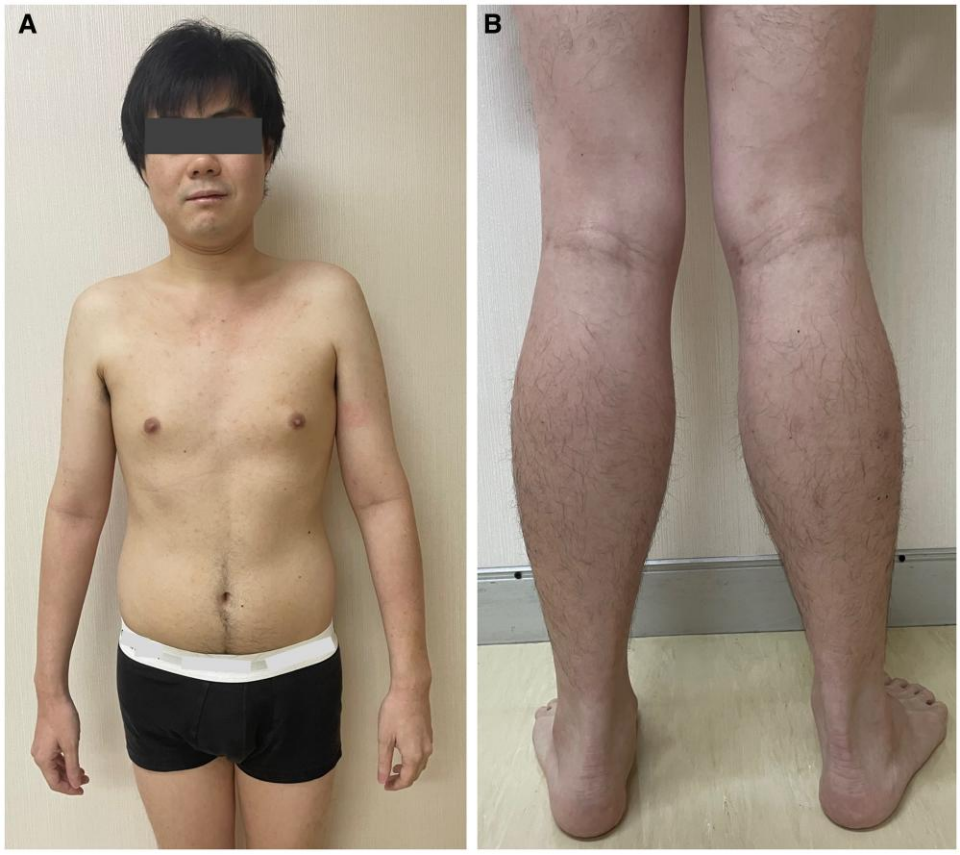

Figure 2. The patient's body habitus revealed (A) abnormal fat accumulation resulting in subcutaneous fat loss in upper arms and (B) atrophy of the thigh muscles contrasting to hypertrophy of the calf muscles.

Discussion

KPD syndrome is characterized by an acute onset of severe hyperglycemia with or without ketoacidosis, which insulin discontinuation could be achieved in most patients after several weeks to months following DKA [13]. A typical patient is male, middle-aged, overweight or modestly obese with a strong family history of diabetes. However, this syndrome is very heterogeneous and could be an initial presentation of any types of diabetes [14]. There are a number of inherited monogenic disorders that can be secondarily associated with diabetes. The presence of KPD as an initial presentation of new-onset diabetes in this patient poses a diagnostic challenge as to whether the 2 incidents are coincidental or related with the underlying of SMA. But patients with SMA often have sarcopenia and insulin resistance [5, 10]. Increasingly, studies in both animal models and clinical cases reported that patients with SMA displayed glucose intolerance and increased ketones production [6-9, 16, 17]. Moreover, the results for genetic testing in this patient excluded the presence of monogenic diabetes and against the risk for T2D. Therefore, our present case suggested that KPD could be an unusual long-term complication of SMA-related metabolic abnormalities.

Muscle is a major target organ for insulin and is the site of the highest glucose uptake in the human body; therefore, patients with muscular atrophies are more prone to diabetes from insulin resistance and increased adipose tissue [18]. Low skeletal muscle mass and myosteatosis that can be genetically determined or caused by increased lipid spillover from dysfunctional adipose tissue could predispose the patients to develop diabetes. Among patients with SMA, there are several metabolic abnormalities including changes in serum fatty acids, reduced muscle carnitine levels and carnitine palmityl transferase activity, and increased ketones production. These changes were not seen in other muscle disorders such as Duchenne muscular dystrophy [6-9]. Moreover, animal models of SMA also highlighted altered pancreatic cell composition with predominance of glucagon-producing α cells, resulting in hyperglucagonemia [8]. As a result, this hormonal imbalance could potentially predispose patients with SMA to develop ketoacidosis in times of stress or infection. This hypothesis was supported with previous case reports of patients with SMA presenting with ketoacidosis in the presence or absence of concurrent diabetes [6, 11, 19, 20]. In individuals who are predisposed to diabetes, β-cell functions could deteriorate rapidly in response to the effects of glucose toxicity but could also quickly recover if glycemia is lowered. The pathogenesis of KPD also involved the abnormality in ketone oxidation [14]. Defects in ketone oxidation and energy production had been shown in the subset of KPD group [21], which were similar to the metabolic abnormalities seen in patients with SMA.

Individuals with SMA type III still retain the ability to walk with no respiratory muscle weakness and could live into adulthood. The possibility of glucose and lipid abnormalities should be considered and diabetes and lipid screening should be monitored periodically to determine the appropriate and timely interventions if required [22]. Nutritional status should be assessed and optimized to prevent further effects of sarcopenia [23]. In patients with SMA who already developed diabetes, the use of insulin sensitizers such as peroxisome

proliferator-activated receptor agonists could theoretically have direct beneficial effects to increase insulin sensitivity. However, additional works are required to understand the pathogenesis of SMA-associated diabetes and determine which therapeutic approach best suits this atypical diabetes.

In conclusion, our present case highlights the possibility of metabolic abnormalities in SMA patients and should be considered among patients who live well into adulthood. Sarcopenia together with alterations in fatty acid and ketone metabolism could lead to KPD as an initial presentation of diabetes among patients with SMA. Although only 2 previous cases of DKA-associated SMA have been reported [11, 12], future cases may reveal additional atypical diabetes phenotypes in associated with SMA in adulthood.

Learning Points

- Recent studies demonstrated that metabolic complications could develop as emerging complications among spinal muscular atrophy (SMA) patients with long-term follow-up.
- Sarcopenia together with aberrant glucose and fatty acid metabolism can predispose SMA patients to develop diabetes and diabetic ketoacidosis.
- Here, we present a patient with SMA type III who presented with ketosis-prone diabetes as an initial presentation of diabetes.
- The possibility of glucose and lipid abnormalities should be considered and diabetes and lipid screening should be surveillance periodically to determine appropriate timely interventions.
- Nutritional status should be assessed and optimized to prevent further effects of sarcopenia.

Contributors

Y.T. contributed to manuscript preparation and submission. S.N. contributed to the manuscript and graphic preparation. Y.T. contributed to the diagnosis and management of the patient and manuscript preparation. K.K. and Y.T. contributed to the discussions. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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