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CASE REPORT
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A case of prohormone convertase deficiency diagnosed with type 2 diabetes

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What is already known on this topic?

- *Prohormone convertase deficiency is characterized by a deficiency of variable levels in all hormone systems.*
- *Postprandial hypoglycemia is a disorder of glucose metabolism reported in this disease.*

What this study adds on this topic?

- *Prohormone convertase deficiency presenting with a diagnosis type 2 diabetes mellitus is a rare condition.*
- *The difference in the patient's clinic may be due to the new genetic mutation.*
- *Our case revealed that a history of recurrent diarrhea in infancy is important in patients with obesity.*

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ABSTRACT

Prohormone convertase 1/3, encoded by the proprotein convertase subtilisin/kexin type 1 gene, is essential for processing prohormones; therefore, its deficiency is characterized by a deficiency of variable levels in all hormone systems. Although a case of postprandial hypoglycemia has been previously reported in the literature, prohormone convertase insufficiency with type 2 diabetes mellitus has not yet been reported. Our case, a 14-year-old girl, was referred due to excess weight gain. She was diagnosed as having type 2 diabetes mellitus based on laboratory test results. Prohormone convertase deficiency was considered due to the history of resistant diarrhea during the infancy period and her rapid weight gain. Proinsulin level was measured as >700 pmol/L(3.60-22) during diagnosis. In genetic analysis, a c.685G> T(p.V229F) homozygous mutation in the PCSK1 gene was detected and this has not been reported in relation to this disorder. In conclusion, patients with recurrent resistant diarrhea during infancy followed by rapid weight gain need to be evaluated with the diagnosis of prohormone convertase deficiency.

Keywords: Diabetes mellitus, obesity, prohormone convertase, PCSK1, resistant diarrhea

Introduction

Prohormone convertase, which is a member of the seven-member subtilisin-like serine endoprotease family, is an enzyme that converts many biologically inactive prohormones into biologically active peptides. The prohormone convertase 1/3 (PC1/3) is encoded by the proprotein convertase subtilisin/kexin type 1 (PCSK1) gene, and is expressed by neuroendocrine cells such as endocrine pancreatic alpha and beta cells, brain, the pituitary gland, adrenal gland, and intestinal L cells (1, 2). Proprotein convertase subtilisin/kexin type 1 is involved in tissue-specific processes of neuropeptide precursors and prohormones such as pro-opiomelanocortin, proinsulin, proglucagon, and other known energy metabolizers (1). Prohormone convertase 1/3 deficiency is an autosomal recessive disorder, which is characterised by a deficiency of variable levels in all these hormone systems. Insulin deficiency and increased proinsulin levels resulting from the inadequate conversion of proinsulin to insulin are diagnostic markers for PC1/3 deficiency. During infancy, prohormone convertase deficiency leads to resistant diarrhea and then obesity develops. However, hypothyroidism, hypocortisolism, postprandial hypoglycemia, diabetes insipidus, hypogonadism, and growth hormone deficiency have been reported in these cases.

In the literature, a case of postprandial hypoglycaemia associated with glucose metabolism has been reported (3). However, no cases of prohormone convertase deficiency presenting with type 2 diabetes mellitus have been reported so far. We aimed to discuss this issue for the first time in a case report of prohormone convertase deficiency along with the diagnosis of diabetes mellitus.

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Case Presentations

A 14-year-old girl was referred to the paediatric endocrine clinic due to excess weight gain. She had been overweight for twelve years. In the infancy period, she was admitted to hospital with watery diarrhea when she was 12 days old and was hospitalized with dehydration and acidosis secondary to diarrhea. It was learned that she had several hospitalizations due to diarrhea. Her body weight was 3.1 kg at 36 days and 3.5 kg at 3.5 months of age. Sufficient weight gain could not be achieved and diarrhea continued until 1 year of age. The patient started to gain weight rapidly after 2 years of age. There was no consanguinity between the parents and there was no individually defined diarrhea in the family history. Although her mother had obesity, there was no family history of diabetes. A physical examination on admission revealed that her height was 148.2 (-2.01 sds), body weight was 99.85 kg (+4.73 sds), body mass index (BMI) was 45.46 kg/m^2 (+4.49 sds), and blood pressure was 120/70 mm Hg. The thyroid gland was non-palpable, pubertal stage was Tanner stage 5. Acanthosis nigricans was present both in the axilla and neck region. Striae were present in the arms, upper legs, and around the waist. Her mother's and father's height was 148 cm (-2.32 sds) and 175 cm (-0.21 sds), respectively, and the mid-parental height was 155 cm (-1.25 sds).

In the laboratory tests, blood glucose level was 258 mg/dL, insulin was 75.1 µIU/mL, and the glycated hemoglobin (HbA1c) level was found as 9.6%. According to these test results, the patient was hospitalized with the diagnosis of diabetes mellitus. In blood glucose monitoring, the fasting blood glucose was 150-200 mg/dL and the postprandial glucose level was 200-300 mg/dL. In addition, the following test results were obtained as C-peptide: 7.21 (0.9-7.1) ng/mL, islet antibody: 0.37 (<1) U/L, anti-GAD antibody: 0.29 (<1) IU/mL, and anti-insulin antibody: 0.73 (<12) U/mL. Diabetic diet and 2x850 mg metformin treatment were initiated with the diagnosis of type 2 diabetes to the patient. Lipid parameters and liver function test results were as follows: cholesterol: 227 (95-237) mg/dL, low-density lipoprotein (LDL) cholesterol: 154 (38-140) mg/dL, high-density lipoprotein (HDL) cholesterol: 37 (>35) mg/dL, triglyceride: 174 (37-131) mg/dL, aspartate aminotransferase (AST): 33 (<47) U/L, and alanine aminotransferase (ALT): 26 (0-27) U/L. Abdominal ultrasonography revealed stage 3 fatty liver. Systolic overload in the daytime and nighttime and diastolic overload in the nighttime were determined in blood pressure monitoring. An angiotensin-converting enzyme (ACE) inhibitor was started as an antihypertensive agent to the patient who had mild hypertrophy on the posterior wall of the left ventricle.

Prohormone convertase deficiency was considered due to the history of treatment-resistant diarrhea in the infancy period and the fact that the patient had started to gain weight after 2 years of age. The proinsulin level at diagnosis was >700 (3.60-22) pmol/L. In genetic analysis, a c.685G> T (p.V229F) homozygous mutation was determined in the PCSK1 gene. However, it should be noted that this mutation has not been reported related to this disorder. It is anticipated to be a pathogenic change by Mutation Taster, one of the silico assessment tools. This mutation was located in the region coding for the catalytic domain of the protein. It is difficult to say whether there was residual activity because functional enzyme analysis could not be performed. Written informed consent was obtained from mother of the patient.

Other hormone insufficiencies probably seen in prohormone convertase deficiency were investigated. To rule out central hypothyroidism, thyroid function tests were evaluated. Thyroid-stimulating hormone (TSH) was 1.79 (0.6-5.5) µIU/L, free T4 was 0.96 (0.8-1.9) ng/dL, and free T3 was 2.97 (2-6.5) pg/mL, all of which were in the normal range. In terms of adrenal insufficiency, baseline cortisol levels and adrenocorticotropic hormone (ACTH) levels were measured, which were found as 6.7 µg/dL and 58.2 pg/mL, respectively. In the low-dose ACTH stimulation test, peak cortisol was found to be normal at 21.4 µg/dL. The patient had no polyuria. The blood sodium (Na) was 138 mg/dL, blood osmolarity was 279 mOsm/kg, urine density was 1032, and urine osmolarity was 798 mOsm/kg, and there was no diabetes insipidus. Follicle-stimulating hormone (FSH) was 3.54 mIU/mL, luteinizing hormone (LH) was 4.4 mIU/mL, and estradiol was 36.64 pg/mL, all of which were in the normal range.

The blood glucose profile improved within 7 days when 1800 caloric diabetic diet and metformin treatment were initiated following the diagnosis of type 2 diabetes. The fasting blood glucose was 99 mg/dL and postprandial blood glucose was 134 mg/dL. Three months after discharge, her weight was 97 kg, fasting blood glucose was 85 mg/dL, the postprandial blood glucose level was 92 mg/dL, HbA1c was 5.6%, and C-peptide was 4.84 ng/mL.

Discussion

Deficiency of prohormone convertase leads to inactivation of many hormones such as proinsulin, POMC, prothyrotrophin-releasing hormone, pro-glucagon, and pro-gonadotropin-releasing hormone (4). In patients with PC1/3 deficiency, there is a clinical picture characterized by a lack of variable levels of all these hormones. In a study of thirteen patients with prohormone convertase deficiency, it was noted that all individuals were born with normal body weight (3.4±0.3 kg), developed diarrhea, dehydration, and metabolic acidosis in the first 2 months of life. In these subjects, diarrhea was not improved by food elimination, even in the case of fasting, so the deficiency was a malabsorption type, similar to ours (3). In this study, infants were treated with prolonged parenteral nutritional therapy and the mean body weight was less than -3 SDS. For the individuals who progressed beyond the early infancy period, body weight increased significantly. At around 6 years of age, all these children were moderately obese and body weight z score was +2, height z score was – 1, and the mean BMI z score was 2.3±0.3. In our case, diarrhea started in the newborn period similar to all of these cases, continued up to an age of one year, and it has been observed that after 2 years of age, the bodyweight increase was prominent.

Although the mechanism of obesity in further ages is not yet clear, it is emphasized that the impairment of hormone processes leading to loss of control in appetite may play a role in the etiology (2). Prohormone convertase 1/3 participates in the POMC process and is effective in polygenic and monogenic obesity (3, 5). Deterioration in the pro-opiomelanocortin pro-

cess may be responsible for the reduction of melanocyte-stimulated hormone, which plays a role in appetite control (2). Pro-opiomelanocortin-derived peptides are key components of the leptin signalling pathway (3). The prohormone convertase 1/3 also has a role in the processes of central orexigenic hormones, NPY, and agouti-related peptide (AgRP), which compete with alpha melanocyte-stimulated hormone for melanocortin receptor (6, 7). The prohormone convertase 1/3-dependent anorexigenic signal, PYY, may play a role in the increase of appetite (8).

When endocrinopathies in prohormone convertase deficiency were evaluated, subjects who had linear growth retardation and growth hormone (GH) deficiency and were administered GH therapy were reported. Central hypogonadism, central adrenal insufficiency, complete or partial central diabetes insipidus and central hypothyroidism have also been reported. It was noted that there were a large number of postprandial hypoglycaemia episodes in eight cases in a study in which 13 cases were examined (3). The reason for postprandial hypoglycaemia in the literature is explained by the fact that the half-life of proinsulin compared with insulin is longer and the plasma concentration is higher after meals (5, 9). In fact, insulin deficiency due to inadequate conversion of proinsulin to insulin is one of the signs of the disease. However, to date, the disorder in glucose metabolism has been reported in only two cases (4, 5). In one of these cases, glucose metabolism was evaluated in the first year of GH therapy for GH deficiency, the fasting blood glucose level was normal, and the blood glucose level at the 2nd hour in the oral glucose tolerance test (OGTT) was found to be in accordance with diabetes. Diabetic diet and physical activity were recommended to the patient who had HbA1c of 5.8% and negative results of diabetic autoantibodies and GH therapy was continued. In this patient with PC1/3 deficiency, HbA1c progressively increased to 10.5% and then blood glucose levels rose to 725 mg/dL with ketoacidosis in the first year of follow-up. After the diabetic ketoacidosis treatment, insulin therapy given at a dose of 1.5 u/kg/day followed by a dose of 0.15 u/kg/day within 10 days, complete insulin withdrawal at 1 month, and normal fasting and postprandial blood glucose levels were observed. In this patient, GH therapy was continued until the age of 15 years and it was reported that the OGTT performance at the age of 17 years was normal. Our patient was diagnosed as having diabetes, similar to this case. In our case, we observed a progressive decrease in blood glucose levels and a rapid normalization of HbA1c with diet and metformin therapy without the occurrence of ketoacidosis. The other patient with glucose metabolism disorder presented with obesity, amenorrhea, and postprandial hypoglycaemia at the age of 43 years. Also, it was reported that diabetes occurred in this case necessitating insulin therapy during pregnancy (5). The PCSK1 gene is located on chromosome 5 (10). This region has been defined to be related to both obesity and type 2 diabetes (11). Variants in the PCSK1 gene encoding PC1/3 contribute to polygenic obesity risk as shown by candidate gene approaches and subsequent genetic association studies as well as genome-wide association studies for BMI and proinsulin (10, 12). Glucose regulates insulin and PC1/3 expression, supporting the important role of PC1/3 in regulating proinsulin processing (11). In our case, proinsulin levels are very high, as expected, but c-peptide is also very high. We used chemiluminescence (CLIA) method for proinsulin measurement and no cross-reaction with insülin and C-peptide has been reported in this method (13). Pepin et al. (14) was stated that the proinsulin level was measured in 15 patients with PC1/3 deficiency and it was between 8 and 154 times acoording to the upper limit of the normal, the median level was 74 pmol/L, and the insülin/proinsulin ratio in 6 patients was 0.068±0.069 SD. In this article, localized PCSK1 pathogenic variants in the region encoding the catalytic domain and P domain of the protein were compared and no genotype-phenotype correlation was found. The absence of cross-reaction in the assay used in our patient and the high level of C-peptide suggests residual PC1/3 activity.

Eighteen patients with PCSK1 deficiency have been reported so far, seven cases (38.8%) including ours were of Turkish origin (1, 3-5, 15). Prohormone convertase deficiency is an autosomal recessive disorder and its high occurrence in our country may be due to the higher frequency of consanguineous marriages. However, there was no consanguinity between the parents of our patient. It should be noted that the underreporting of the disease in the world literature may be related to a lack of awareness of this disease in physicians. Patients may have died from recurrent diarrhea episodes during infancy. Indeed, in the literature, three patients died during infancy (3, 9). In one of the studies, three of the patients had siblings with similar clinics and it was reported that they died before diagnosis (3). The sister of our patient died from an unknown reason in the postnatal third month. We think that there will be more data about the disorder, when the awareness of it increases. For this reason, we wanted to report this case, which has rarely been discussed in the literature.

We conclude that it is important for pediatricians to consider the diagnosis of prohormone convertase deficiency in infants with recurrent resistant diarrhea during infancy. Moreover, if obesity develops after childhood and there are recurrent serious diarrhea episodes in the patient history, this diagnosis should be considered. We recommend that other hormone deficiencies should be screened in patients with a definite diagnosis of proinsulin elevation and/or genetic analyses should be made.

Informed Consent: Written informed consent was obtained from patient's family who participated in this study.

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