

Latent Autoimmune Diabetes in Adults Complicated by Persistent Isolated Glucosuria in the Absence of Hyperglycemia

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Abstract

Latent autoimmune diabetes in adults (LADA) is an autoimmune diabetes of adult-onset with the presence of diabetes associated autoantibodies. Familial renal glucosuria (FRG) is an inherited renal tubular disorder that causes persistent isolated glucosuria in the absence of hyperglycemia. We report a novel case of LADA and certain FRG. A 44-year-old man was admitted to our hospital for uncontrolled diabetes. Before admission, he had never suffered from diabetic coma and showed an improvement in HbA1c only with diet therapy. His HbA1c was 11.9% (107 mmol/mol), and anti-glutamic acid decarboxylase antibody was 13.0 U/mL. A glucagon stimulation test showed the decrease of insulin secretion: plasma C-peptide (CPR) 0 min, 0.69 ng/mL; CPR 6 min, 0.90 ng/mL. Analysis of genomic DNA revealed a novel heterozygous mutation in the SGLT2 coding gene, *SLC5A2* (c.875G >A, p.Cys292Tyr), which was assessed as probably damaging with a score of 0.998 (sensitivity: 0.27; specificity: 0.99) by an *in silico* analysis. Therefore, he was diagnosed with LADA and certain FRG. He has not shown any symptoms and his HbA1c improved to 6.4% (46 mmol/mol) three months after the introduction of insulin therapy. Our case clearly implies the clinical effectiveness of SGLT2 inhibition in patients with LADA.

Keywords

Latent Autoimmune Diabetes in Adults (LADA), Familial Renal Glucosuria (FRG), *SLC5A2* Mutation, Sodium-Glucose Cotransporter 2 (SGLT2), Insulin Therapy

1. Introduction

Latent autoimmune diabetes in adults (LADA) accounts for 2% - 12% of all cases

of diabetes [1] [2]. It is important to distinguish LADA from type 2 diabetes because patients with LADA have a higher probability of requiring insulin therapy due to a relatively rapid deterioration of pancreatic β -cell function compared to patients with type 2 diabetes [2]. Familial renal glucosuria (FRG) is an inherited renal tubular disorder that causes persistent isolated glucosuria in the absence of hyperglycemia [3]. It has been known that mutations in the sodium-glucose co-transporter 2 (SGLT2) coding gene, *SLC5A2*, were responsible for the disorder [4]. Herein, we report a novel case of LADA and certain FRG.

2. Case Report

A 44-year-old man was admitted to our hospital for uncontrolled diabetes for two years. His HbA1c was 12.0% (108 mmol/mol) 18 months before admission, which improved to 6.4% (46 mmol/mol) following a diet therapy for six months, and deteriorated to 12.0% (108 mmol/mol) again three months before admission. The patient had symptoms of polyuria, polydipsia, and unintended weight loss (8 kg/year). His past medical history was unremarkable and he had not taken any medication. However, the patient, his mother, and his 14-year-old son repeatedly presented with glucosuria despite normal blood glucose concentrations in their annual health check-up. There was no family history of diabetes. At the time of admission, his height was 168 cm and his weight was 57 kg; his blood pressure was normal. The patient presented with the following levels: HbA1c, 11.9% (107 mmol/mol); and anti-glutamic acid decarboxylase (GAD) antibody (measured with an enzyme linked immunosorbent assay), 13.0 U/mL (normal range, <5.0 U/mL). A glucagon stimulation test revealed the following results: plasma C-peptide (CPR) 0 min, 0.69 ng/mL; CPR 6 min, 0.90 ng/mL; plasma glucose (PG) 0 min, 102 mg/dL; PG 6 min, 123 mg/dL. He was diagnosed with LADA and was initiated on intensive insulin therapy with alpha-glucosidase inhibitors to preserve β -cell function [5]. His human leukocyte antigen (HLA) class II haplotypes were *DRB1* *04:05-*DQB1* *04:01, which was concordant with the diagnosis of LADA [6]. PG was controlled to an average of 150 mg/dL by an insulin injection and was monitored using continuous glucose monitoring. Urinary glucose and sodium levels were 15.8 g/day and 114.1 mEq/day. Analysis of genomic DNA from his blood samples revealed a novel heterozygous *SLC5A2* mutation (c.875G>A, p.Cys292Tyr). Therefore, the patient was also diagnosed with certain FRG. He has not shown any symptoms and his HbA1c improved to 6.4% (46 mmol/mol) three months after the introduction of insulin therapy.

3. Discussion

To the best of our knowledge, this is the first case report of LADA complicated by persistent isolated glucosuria in the absence of hyperglycemia. We thought that his persistent isolated glucosuria due to mutations in the SGLT2 coding gene, *SLC5A2*, assisted in maintaining glycemic control and pancreatic β -cell function.

LADA is an autoimmune diabetes of adult-onset with the presence of diabetes associated autoantibodies, which may not initially require insulin therapy [1] [2]. Turner *et al.* showed that 94% of patients with LADA required insulin therapy by 6 years, and time to insulin dependence was more rapid in patients <45 years old than in older cases [7]. The other previous study showed that the degrees of autoimmunity and loss of β -cell function were related to the need for insulin therapy [8]. However, to date, the treatment in patients with LADA has not been established: the clinical effectiveness of early introduction of insulin therapy for them is still controversial [2].

FRG is characterized by abnormal urinary glucose excretion in the absence of hyperglycemia [3]. It is a rare disease caused by an isolated renal tubular disorder, not accompanied by other proximal tubular transport abnormalities and renal dysfunction [3]. Therefore, patients with FRG are generally asymptomatic, and do not need medical intervention. The *SLC5A2* mutation has been confirmed to be responsible for the large majority of FRG, which explains the mechanism of FRG as a result from a defect in SGLT2 [9]. Although the *SLC5A2* mutation (c.875G > A, p.Cys292Tyr) in the present case has not been reported in patients with FRG, it was assessed as probably damaging with a score of 0.998 (sensitivity: 0.27; specificity: 0.99) by an *in silico* analysis.

Fortunately, our patient had never suffered from diabetic coma and showed improvement in HbA1c only with diet therapy, despite decreased insulin secretion. Considering that it has been recently reported that SGLT2 inhibitors have a positive effect on pancreatic β -cell function and glycemic control even in patients with type 1 diabetes as well as type 2 diabetes [10] [11], we assumed that SGLT2 inhibition might have some effective role for his clinical course. Further clinical and pathological studies are needed to clarify this effectiveness.

4. Conclusion

We experienced a novel case of LADA complicated by persistent isolated glucosuria in the absence of hyperglycemia. Our case clearly implies the clinical effectiveness of SGLT2 inhibition in patients with LADA.

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