

Juvenile case with the coexistence of maturity-onset diabetes of the young 1 and later-onset latent autoimmune diabetes in youth

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Keywords

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ABSTRACT

We present the case of a 12-year-old Japanese girl, who was positive for markers of both maturity-onset diabetes of the young and latent autoimmune diabetes in youth. She was initially diagnosed with maturity-onset diabetes of the young 1 based on the molecular analysis, and she later developed an autoimmune response, leading to β -cell-associated antibody-positive diabetes. She was treated with incretin-associated drugs and maintained adequate glycemic control. Pathophysiologically, there was an overlap between the two different types of diabetes, because the hyperglycemia and β -cell stress seen in non-autoimmune diabetes can cause β -cell autoimmunity over time.

INTRODUCTION

Maturity-onset diabetes of the young (MODY) is characterized by autosomal dominant inheritance onset before 25 years-of-age and the absence of β -cell autoimmunity¹. Mutations related to MODY have been reported in at least 14 different genes. MODY is a rare condition, accounting for 1–5% of all cases of diabetes^{2,3}.

The pathophysiology of MODY is very different from that of autoimmune diabetes. However, some reports have shown the coexistence of MODY and autoimmune diabetes. As for the frequency of antibody detection in MODY, McDonald *et al.*⁴ reported that the prevalence of β -cell-associated autoantibodies was the same as in control individuals (<1%). Whereas, Schober *et al.*⁵ and Urbanová *et al.*⁶ reported higher frequencies of the autoantibodies (17% and 25%). We found no report describing the coexistence of MODY and autoimmune diabetes in Japanese individuals.

We encountered a case of overlapping MODY and latent autoimmune diabetes in youth (LADY)⁷, which was initially diagnosed as MODY1 based on the molecular analysis, and was later changed to β -cell-associated antibody-positive diabetes during the course of diabetes.

CASE REPORT

The patient was a 12-year-old Japanese girl. She was referred to the Nihon University School of Medicine Hospital, Tokyo, Japan, after the detection of glycosuria by the screening program at her school. Blood investigations showed fasting plasma glucose level of 209 mg/dL (11.6 mmol/L) and glycated hemoglobin of 10.5% (90 mmol/mol), which was consistent with the diagnosis of diabetes. She was born at 39 weeks of gestational age and weighed 3,422 g. She had no medical history of persistent hyperinsulinemic hypoglycemia during infancy. Her parents had no diabetes; however, her paternal uncle was clinically diagnosed with type 2 diabetes (Figure 1). Her height was 148.9 cm, weight 38.1 kg and body mass index 17.2 kg/m². We carried out a glucagon stimulation test, and the baseline C-peptide level was 1.4 ng/mL (0.5 nmol/L), the C-peptide level after 6 min was 3.2 ng/mL (1.1 nmol/L) and the peak C-peptide level was 3.2 ng/mL (1.1 nmol/L). There were no β -cell-associated autoantibodies including insulin autoantibody, glutamic acid decarboxylase, tyrosine phosphatase-like insulinoma antigen 2 (IA-2) and β -cell-specific zinc transporter 8 antibodies. Human leukocyte antigen typing was not susceptible to haplotypes for type 1 diabetes in the Japanese population. Based on these results, molecular analyses for MODYs were carried out, which showed a novel

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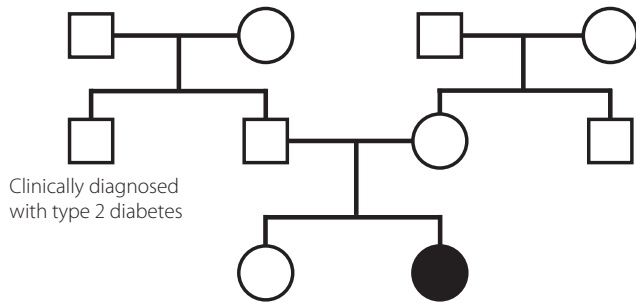


Figure 1 | Family pedigree of the patient.

heterozygous missense mutation c.940C>T (p.Gln314*) in exon 8 of the hepatocyte nuclear factor 4 α gene. The patient was finally diagnosed as a case of MODY1.

The patient's plasma glucose levels were initially under good control with insulin treatment, but she experienced bouts of hypoglycemia at times. After confirmation of the diagnosis of MODY1, the treatment was switched from insulin to oral hypoglycemia drugs, comprising a dipeptidyl-peptidase-4 inhibitor, alogliptin 12.5 mg/day and a sulfonylurea, glimepiride 0.5 mg/day. After this change in treatment, the bouts of hypoglycemia decreased, and she maintained glycated hemoglobin levels between 7 and 7.5% (52–58 mmol/mol; Figure 2).

After 3 years from the diagnosis, an antibody test showed that the IA-2 antibody had changed to positive; a titer of 3.4

U/mL was detected (by a radioimmunoassay method). Other autoantibodies remained negative. On glucagon stimulation test, the baseline C-peptide level was 1.46 ng/mL (0.5 nmol/L), the C-peptide level after 6 min 2.09 ng/mL (0.7 nmol/L) and the peak C-peptide value 2.56 ng/mL (0.85 nmol/L). We changed the treatment from alogliptin and glimepiride to a glucagon-like peptide-1 agonist, liraglutide 0.9 mg, because her glycemic control was poor. Subsequently, the glycated hemoglobin levels were maintained at approximately 6% without episodes of hypoglycemia. The IA-2 antibody continued to be positive on radioimmunoassay and on enzyme-linked immunosorbent assay during the course of the study (Figure 1). From the clinical course, we diagnosed her with later-onset autoimmune diabetes, LADY.

DISCUSSION

MODY1 is a relatively uncommon subtype of MODY, accounting for approximately 5% of all MODY cases. MODY1 is phenotypically similar to MODY3, and manifests as a gradual decrease in endogenous insulin secretion and the development of diabetes in adolescence^{2,3}. Patients with MODY3 and MODY1 are usually sensitive to sulfonylureas^{2,3}. Another therapeutic means is a glucagon-like peptide-1 receptor agonist, which can increase endogenous insulin secretion proportionate to plasma glucose levels, and decrease glucagon release with a low risk of hypoglycemia. Additionally, they possibly prevent β -

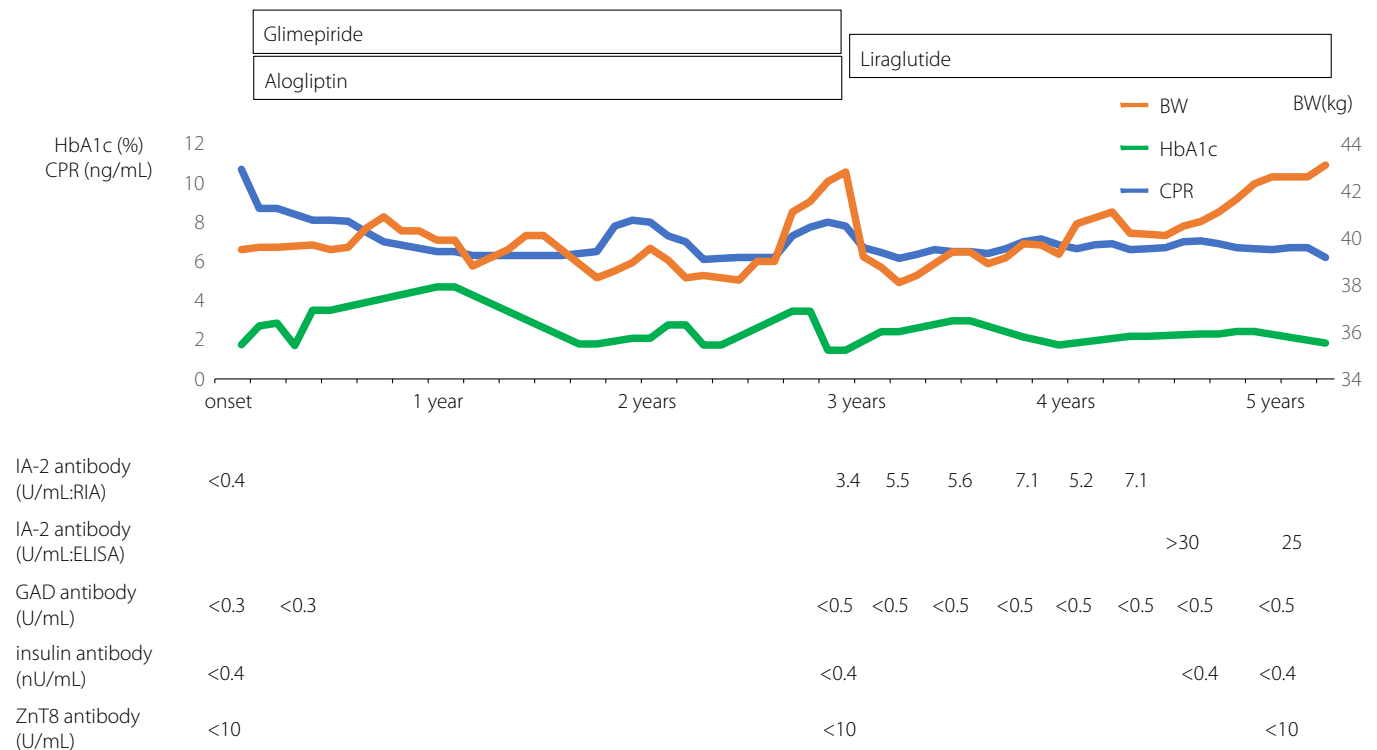


Figure 2 | Clinical course and changes in β -cell-associated autoantibodies. BW, bodyweight; CPR, C-peptide; ELISA, enzyme-linked immunosorbent assay; GAD, glutamic acid decarboxylase; HbA1c, glycated hemoglobin; IA-2, insulinoma antigen 2; RIA, radioimmunoassay; ZnT8, zinc transporter 8.

Table 1 | Clinical features in β -cell-associated autoantibody-positive cases with maturity-onset diabetes of the young

| Case | Mutation | HbA1c at diagnosis (%) | Autoantibody | Age at diagnosis (years) | Duration (years) | Initial treatment | BMI at diagnosis | Current treatment | Time to insulin (duration of insulin) | onset | Family history |
|------|---------------------------------------|------------------------|---------------------------|--------------------------|------------------|-------------------|------------------|------------------------------------|---------------------------------------|--|---|
| 1 | <i>HNF4A</i> missense mutation exon 8 | 10.5 | IA-2 3.4 (units/mL) | 12 | 3 | Insulin | 17.2 | Liraglutide: 0.9 mg | At diagnosis (for 1 month) | Detection by urine glucose screening at school | Paternal uncle (clinically type 2 diabetes) |
| 2 | <i>HNF1A</i> R272H | 7.2 | GAD >250 (WHO – units/mL) | 31 | 7 | Diet | 22.6 | Repaglinide: 0.5mg after each meal | No insulin | Gestational diabetes | Three-generation |
| 3 | <i>HNF1A</i> R203H | 7.4 | GAD >250 (WHO – units/mL) | 32 | 4 | Insulin | 26.9 | Insulin: basal–bolus regimen | At diagnosis (continued) | Hyperglycemia after urinary tract infection | Three-generation |
| 4 | <i>HNF1A</i> R577D | 6.7 | GAD >234 (WHO – units/mL) | 14 | 39 | Insulin | 25.0 | Insulin: basal bolus regimen | At diagnosis (for 1 month) | Acute onset | Three-generation |
| 5 | <i>GCK</i> V182M | 7.9 | GAD >250 (WHO – units/mL) | 29 | 47 | Diet/OHA | 26.0 | Insulin: premixture insulin | At 10-year (continued) | Casual detection asymptomatic | Two-generation |
| 6 | <i>GCK</i> deletion exons 5 and 6 | 8.1 | GAD >250 (WHO – units/mL) | 1 | 3 | Insulin | 16.6 | Insulin: CSII | At diagnosis (continued) | Acute onset | Three-generation |

BMI, body mass index; GAD, glutamic acid decarboxylase; HbA1c, glycated hemoglobin; HNF, hepatocyte nuclear factor; IA-2, insulinoma antigen 2; OHA, oral hypoglycemic agent; WHO World Health Organization.

cell apoptosis and promote β -cell generation in MODY3 and MODY1³. Therefore, glucagon-like peptide-1 receptor agonists might be appropriate alternatives to sulfonylureas in the treatment of MODY1, as well as MODY3, only when endogenous insulin secretion is preserved. We checked the MODY genes in the patient's parents, but we found no mutations. Therefore, we considered the patient's mutation as de novo.

LADY is caused by β -cell autoimmunity⁷; this pathophysiology is quite different from that of MODY. However, some reports of studies carried out with people of European descent showed a high prevalence of β -cell-associated autoantibodies in MODY patients^{5,6,8,9} (Table 1). As for MODY1 patients, McDonald *et al.*⁴ reported that none of the 52 patients had β -cell-associated autoantibodies, and Urbanová *et al.*⁶ showed that two out of the five Czech patients were positive for the autoantibodies. Interestingly, the majority presenting with MODY and autoimmune diabetes markers showed no clinical features of autoimmune diabetes, without a significant decline in endogenous insulin secretion other than with positive β -cell-associated autoantibodies⁶. In the present patient, she initially maintained optimal glycemic control during a long period with oral hypoglycemic drugs. She aggravated the glycemic control after the appearance of IA-2 antibodies. However, she maintained endogenous insulin secretion under treatment with liraglutide, which might help to improve glycemia and to preserve β -cell function.

We hypothesize the possible mechanisms in the coexistence of MODY1 and autoimmune diabetes as follows: patients with MODY1 develop impaired β -cell function leading to hyperglycemia. Hyperglycemia can contribute to β -cell autoimmunity and concomitant innate immune activation within the islet initiates β -cell-specific cytotoxic T lymphocyte responses, which further damages the beleaguered β -cells¹⁰. These mechanisms can cause autoimmune destruction of the β -cells in MODY1 patients.

In conclusion, the two different types of diabetes, MODY and LADY, could coexist over time, because hyperglycemia and β -cell stress, observed in non-autoimmune diabetes, can cause β -cell autoimmunity, leading to the development of autoimmune diabetes. It is necessary to examine the β -cell-associated autoantibodies over time in patients with any type of diabetes when there is a drop in endogenous insulin secretion.

DISCLOSURE

The authors declare no conflict of interest.

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