

Maternally Inherited Diabetes and Deafness (MIDD) with Undetectable C-Peptide Level and Cerebellar Atrophy

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Abstract

Maternally inherited diabetes and deafness (MIDD), also called mitochondrial diabetes mellitus, is a rare form of diabetes that comprises 0.5-2.8% of the diabetic population. Most cases of MIDD are associated with a point mutation in the mitochondrial DNA (mtDNA) at position 3243 of the leucine tRNA gene (A3243G). Patients with MIDD are characterized by 1) young onset of diabetes, 2) absence of obesity, 3) neurosensory hearing loss, 4) maternal family history of diabetes and 5) progressive insulin secretory defect. In most cases of MIDD, diabetes is non-insulin dependent at onset, but progresses to require insulin therapy thereafter. However, to our knowledge, few cases with MIDD show complete loss of C-peptide level during the course of the disease.

Keywords: Mitochondrial diabetes; Beta cell function; Japanese

Abbreviations

MIDD: Maternally Inherited Diabetes and Deafness; CPR: C-Peptide immunoreactivity; GAD: Glutamic Acid Decarboxylase; IA-2: Insulinoma-Associated protein-2; MRI: Magnetic Resonance Imaging; IVGTT: Intravenous Glucose Tolerance Test

Case Report

Maternally Inherited Diabetes and Deafness (MIDD), also called mitochondrial diabetes mellitus, is a rare form of diabetes that comprises 0.5-2.8% of the diabetic population [1-4]. Most cases of MIDD are associated with a point mutation in the mitochondrial DNA (mtDNA) at position 3243 of the leucine tRNA gene (A3243G) [2-4]. Patients with MIDD are characterized by 1) young onset of diabetes, 2) absence of obesity, 3) neurosensory hearing loss, 4) maternal family history of diabetes and 5) progressive insulin secretory defect [1-3,5]. In most cases of MIDD, diabetes is non-insulin-dependent at onset, but progresses to require insulin therapy thereafter. However, to our knowledge, few cases of MIDD show complete loss of C-peptide during the course of the disease.

The case was a 42-year-old Japanese man. At the age of 34, he attended our clinic because of thirst, polydipsia and weight loss (5 kg in 6 months), and was diagnosed with diabetes (plasma glucose 436 mg/dl, HbA1c 18.2%). He showed a short, lean stature (1.54 m, 41 kg, BMI 17.3) and had had neurosensory hearing loss since childhood treated with a hearing aid. His mother also had diabetes and hearing loss, and he showed mtDNA A3243G mutation. Islet-related autoantibodies (glutamic acid decarboxylase (GAD) and insulinoma-associated protein-2 (IA-2) antibodies) were negative. He was diagnosed with MIDD and insulin therapy was started. Under basal-bolus insulin therapy, his HbA1c level decreased to ~7%. He also had an older sister with hearing loss but not diabetes, although it was not possible to perform genetic testing in his family members.

At the time of diagnosis, serum C-peptide immunoactivity (CPR) level was 1.1-5.3 ng/ml. However, CPR level gradually declined and became undetectable (<0.05 ng/ml) from the age of 38. Although HbA1c level remained at 7-8%, he was admitted to our hospital at the age of 42 because of repeated episodes of hypoglycemia. At this time, he was treated with insulin lispro 5 U before each meal and insulin glargine 7 U at bedtime. He had neither diabetic retinopathy nor macular pattern dystrophy, but had microalbuminuria (32.7 mg/g creatinine) and diabetic neuropathy. Serum CPR and 24 h urinary CPR were both undetectable (<0.05 ng/ml and <2 µg/day, respectively). While chest X-ray and electrocardiogram were normal, brain magnetic resonance imaging (MRI) revealed cerebellar atrophy. No other abnormality such as basal ganglia calcification was detected. Continuous Subcutaneous Insulin Infusion (CSII) was introduced to prevent hypoglycemia.

Although, in general, patients with MIDD show lower insulin secretory capacity and need insulin therapy to manage hyperglycemia, usually they retain some residual CPR level [1]. Hosszufalusi et al. reported that there is a loss of first phase and total CPR response but measurable fasting CPR (0.79-6.57 ng/ml) during an intravenous glucose tolerance test (IVGTT) in patients with MIDD compared with nondiabetic controls [6]. Guillausseau et al. reported that 17% of patients with MIDD were insulin-dependent from the onset, with ketoacidosis in 8% of patients, while in the others (83%) diabetes resembled type 2 diabetes [7], suggesting that there is heterogeneity of the diabetic phenotype in patients with MIDD, although the CPR levels of the patients were not reported. The severity of the phenotype in patients with MIDD may be associated with the degree of heteroplasmy [8] and glucose intolerance of their mothers [1].

In the present case, maternal diabetes, younger age of onset, lean stature and presence of other neurological abnormalities were consistent with the severe phenotype of MIDD. However, an undetectable CPR level is rarely seen in patients with MIDD and it is possible that his condition might have been complicated by type 1 diabetes, even though GAD and IA-2 antibodies were negative. Heterogeneity of the phenotype of MIDD may not only be associated

with the degree of heteroplasmy, but also confounded by environmental or other genetic factors and possibly the coincidence of other types of diabetes.

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