Maternally Inherited Diabetes with Deafness and Obesity: Body Weight Reduction Response to Treatment with Insulin Analogues

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Abstract

Maternally inherited diabetes with deafness (MIDD) is a rare, monogenic form of diabetes mellitus caused by mutations in the mitochondrial genome, the most frequent being the A3243G substitution of the tRNA^Leu^ gene. We screened 520 individuals with type 2 diabetes mellitus and 45 probands from families with a clinical picture of maturity onset diabetes of the young (MODY) using restriction fragment length polymorphism. We used the following primer pair: forward - 5’ AAGGTTCGTTTGTTC

Case report

Maternally inherited diabetes with deafness (MIDD) is a rare, monogenic form of the disease caused by mutations in the mitochondrial genome, most frequently the A3243G tRNA^Leu^ substitution [1, 2]. Impaired pancreatic β-cell insulin secretion is its major pathophysiological mechanism. MIDD is characterized by variability in clinical presentation, as it may mimic type 1 as well as type 2 diabetes [2]. The disease is usually diagnosed in early adulthood; however the range of age of onset is wide.

We screened for the A3243G tRNA^Leu^ substitution in 520 unrelated individuals with a clinical diagnosis of type 2 diabetes and 45 probands of maturity onset diabetes from young (MODY) families using restriction fragment length polymorphism. We used the following primer pair: forward - 5’ AAGGTTCGTTTGTTC
We identified just one mutation carrier, a 20-year-old woman who was a proband from a family from the MODY registry, diagnosed at the age of 16 years. She was also diagnosed with early stage hypoacusis, macular pattern dystrophy, hypertension, and mild depression. The only family member available for the study was her 50 year-old mother, who had been diagnosed at the age of 35 and treated with insulin since diagnosis. We confirmed the presence of the A3243G point mutation in the proband’s mother. The family pedigree is shown in Figure 1. The detailed clinical characteristics of the patients are presented in Table 1.

Interestingly, the proband was characterized by abdominal obesity, an uncommon condition in MIDD. Her body mass index was 32.0. In spite of long-term suggestions to reduce her obesity and repeated dietary advice, she was unable to reduce her weight. At the initial examination, she was treated by a multiple daily injection (MDI) regimen based on regular human insulin and neutral protamine Hagedorn insulin as basal insulin. She received 1 U of insulin/kg daily and her HbA1c was 7.2%. In addition, ultrasonography revealed asymptomatic gallstones. The surgeon suggested weight reduction before cholecystectomy.

Weight reduction is a challenge for diabetic patients on insulin. Moreover, metformin is considered to be contraindicated in MIDD patients because of the potential risk of lactate acidosis [2]. Initially, this woman’s lactate level was 2.2 mmol/l, slightly above the upper limit of the reference range (2.1 mmol/l). Multiple injections of aspart, a short-acting insulin analog, were administered together with one evening injection of detemir, a long-acting insulin analog. The woman was also instructed to maintain a

![Figure 1. The MIDD family pedigree.](image-url)
diet of 1200 kcal, the regimen previously recommended. At 3-month follow-up her weight had decreased by 6.3 kg and the daily insulin dose had fallen by 30 U. These changes were accompanied by a decrease in HbA1c level to 6.1%, while lactate level remained stable. Having achieved substantial weight reduction, she underwent successful cholecystectomy.

Nowadays, identification of the molecular background of specific forms of diabetes supplies new insight into their underlying etiology. This should help to optimize treatment in specific clinical situations, which is an essential aspect of pharmacogenetics, including avoidance of medications that might be harmful in particular forms of diabetes. Metformin is not recommended for safety reasons in MIDD associated with obesity, so we used an MDI regimen based on insulin analogues. This algorithm showed a favorable impact on body weight, as compared to traditional insulins, in patients with both type 1 and type 2 diabetes [3, 4]. On the basis of this case, we suggest that this regimen, together with appropriate dietary advice, should be a preferred therapeutic option in certain other rare clinical situations, such as MIDD associated with obesity.

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References


