The Review of DIABETIC STUDIES

CASE REPORT

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. One carrier of the mutation being investigated was found in a proband from a MODY family. The patient was a 20 year-old woman, diagnosed at the age of 16 years as having type 1 diabetes mellitus. On entry to the study, she was treated by a multiple daily injection regimen (MDI) with regular human insulin and human NPH insulin. Typical extra-pancreatic symptoms of MIDD were present, such as macular pattern dystrophy and mild bilateral sensory hearing loss. Additionally, the patient presented abdominal obesity (BMI 32.0), an uncommon feature in monogenic insulin secretion defects, including MIDD. To facilitate weight loss, the diabetes treatment was modified. Since metformin treatment is considered to be contraindicated in MIDD because of the increased risk of lactic acidosis, we used insulin analogues (aspart and detemir) in an MDI regimen and hypocaloric diet. This resulted in a 6.3 kg weight reduction (BMI 27.4) and normalization of HbA1c level (from 7.2 to 6.1 %) during a three-month follow-up. On the basis of this case, we suggest that an MDI regimen with insulin analogues may be a preferred therapeutic option in some rare clinical situations, such as MIDD associated with obesity.

Keywords: MIDD · diabetes · mitochondrial genome · obesity · insulin analogues

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

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Table 1. Clinical characteristics of the MIDD patients

Parameter	Patient ID	
	M021-1	M021-2
Age at examination (yr)	20	50
Age at diagnosis (yr)	16	35
Gender	Female	Female
Weight (kg)	74	46
Height (cm)	152	154
BMI (kg/m^2)	32.0	19.4
WHR	0.94	0.86
HbA1c (%)	7.20	8.00
Total cholesterol (mmol/l)	4.14	6.34
HDL cholesterol (mmol/l)	1.52	2.03
LDL cholesterol (mmol/l)	2.01	3.74
Triglycerides (mmol/l)	1.34	1.25
C-peptide (ng/ml)	1.09	0.92
Serum urea (mmol/l)	3.90	6.60
Creatinine (μmol/l)	62.7	76.9
Urine albumin/creatinine ratio (mg/mmol)	1.91	0.71
Diabetes treatment	Insulin therapy since diagnosis	Insulin therapy since diagnosis
Insulin dose (U/day)	77	60
Diabetic retinopathy (DR)	None	Nonproliferative DR
Macular pattern dystrophy	Present	Present
Audiometry	Early stage bilateral hypoacusis	Moderate bilateral hypoacusis
Hypertension	Present	Present

Legend: BMI: body mass index. WHR: waist-to-hip ratio.

AACGA 3', reverse - 5' AGCGAAGGGTTGTAGTAGCC3' and Bsp120I restriction endonuclease (Fermentas). All subjects were Caucasian residents of Poland. This study was performed according to the Helsinki Declaration with the approval of the Ethics Committee of the Jagiellonian University Medical College. All of the individuals included in this study gave informed consent prior to inclusion.

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

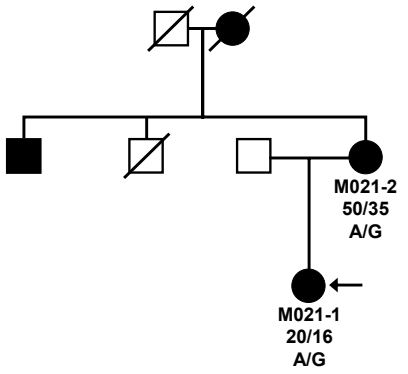

Figure 1. The MIDD family pedigree. Closed and open symbols represent subjects with diabetes and normal glucose tolerance respectively. The numbers indicate patient's ID according to the Polish Registry of MODY Families, age at examination / age at diagnosis of diabetes and genotype at the 3243 position in the mitochondrial genome. The arrow indicates the proband.

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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