Impaired Glucose Effectiveness in Chronic Progressive External Ophthalmoplegia

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Mitochondrial gene mutations have been recognized to be associated with diabetes mellitus. The incidence of diabetes mellitus in patients with other mitochondrial diseases, such as chronic progressive external ophthalmoplegia (CPEO), seems to be several times higher than in the normal population. The aim of the present investigation was to study insulin sensitivity index (SI), insulin secretion ($AIR_{Glucose}$), and glucose effectiveness (Sg) in patients with CPEO. Six unrelated patients with CPEO and 6 matched-pair, unrelated, healthy control subjects underwent a modified intravenous glucose tolerance test (IVGTT) (Bergman's minimal model). Three patients demonstrated an impaired glucose tolerance (IGT), 1 patient already had diabetes mellitus. No significant difference between patients and controls could be demonstrated for SI, $AIR_{Glucose}$, or fasting insulin. However, there was a significant difference for glucose effectiveness Sg ($P = .016$) indicating an impaired glucose effectiveness in the CPEO patients. The diabetic patient showed insulin resistance, low $AIR_{Glucose}$, and low Sg. We conclude that there is a high incidence of IGT and diabetes mellitus in patients with CPEO. Impaired glucose effectiveness seems to play a major role in early pathogenesis. Overt diabetes in CPEO seems to be a combination of insulin resistance, an insulin secretion defect, and impaired glucose effectiveness.

SINCE THE FIRST reports about diabetes mellitus associated with mitochondrial gene abnormalities in 1992,[1-3] a large number of studies have been performed to clarify the pathogenesis of this new diabetes subtype. However, whether insulin resistance or a secretory defect of the pancreatic beta cells is a causative factor has not yet been clarified.[3-10] So far, most of the studies were concerned with the A to G transition at position 3243 in the mitochondrial $tRNA^{Leu(UUR)}$ gene (3243 bp mutation). Very little, however, is known about diabetes mellitus in other mitochondrial diseases, for example, Kearns-Sayre syndrome (KSS) or chronic progressive external opthalmoplegia (CPEO). Like all mitochondrial diseases, CPEO is clinically variable. Ophthalmoplegia (paralysis of the eye muscles), ptosis (droopy eyelids), and limb myopathy are the main clinical features; but there are often additional clinical features, such as cardiac conduction defects, cardiomyopthy, acquired hearing loss, pigmentary retinopathy, short stature, dementia, hypoparathyroidism, or diabetes mellitus.[11-13] Elevated lactate levels in blood, as well as in cerebrospinal fluid, is a key feature of mitochondrial diseases.[14] The so-called "common-deletion", a 4977-bp deletion of the mtDNA is found in muscle tissue in about 50% of sporadic CPEO cases. The typical histopathologic findings are the so-called "ragged-red fibers" (RRFs), which represent accumulations of mitochondria.[13] In contrast to the 3243-bp mutation, which is maternally inherited, CPEO almost always occurs sporadically. The mechanism by which the deletion is caused, however, is not yet known.[13,14]

Although the incidence of diabetes mellitus in patients with CPEO seems to be several times higher than in the normal population,[15,16] little data is available to date with regard to insulin sensitivity and insulin secretion in these patients. The aim of the present study was to investigate CPEO patients with normal glucose tolerance (NGT), as well as in the prediabetic state, and with overt diabetes mellitus with regard to insulin sensitivity and insulin secretion.

SUBJECTS AND METHODS

Patients

Six unrelated patients of Caucasian origin (2 men, 4 women) with the clinical symptoms of CPEO were included in the study. All of them had typical symptoms, such as ptosis and proximal limb weakness. Baseline characteristics are shown in Table 1. One patient was diabetic for 5 years and had been treated with an oral agent (sulfonylurea). Five patients were treated with ubiquinone (150 mg/d) for at least 6 months. Questionnaires were used to ascertain the presence of hypertension, hyperuricemia, and a family history of diabetes. Onset and severity of neurologic symptoms were elucidated in the outpatient clinic of the Department of Neurology of the University of Giessen, Germany (see Table 1). In all 6 patients, a muscle biopsy of the left biceps brachii or deltoid muscle had been performed for light microscopy and molecular analysis (for further details, see Damian et al[17]).

A total of 64 healthy, unrelated individuals with no family history of diabetes mellitus were used as controls. As there was a statistically significant difference for age and body mass index (BMI) between patients and the control group, matched-pairs for gender, age, and BMI were selected from the control group. The average age of the matched-pair control group was 57 years (39 to 71), and their average BMI was 24.7 kg/m^2 (23.1 to 33.6 kg/m^2). The study protocol was approved by the Ethic Committee of the University Hospital of Giessen.

Study Protocol

All patients and controls underwent an intravenous glucose tolerance test (IVGTT) with minimal model analysis between 7:30 and 8:30 AM after a 10-hour overnight fast. An intravenous catheter was placed in an antecubital vein for the administration of medications and for blood sampling. Baseline blood samples for insulin and glucose levels were drawn 10 minutes and immediately before the IVGTT. Fasting cholesterol, triglycerides and C-peptide, glycosylated hemoglobin (HbA_{1c}), creatinine, islet cell antibodies (ICA), and insulin autoantibodies (IAA) were determined. Afterwards, glucose was injected as a 50% solution (0.33 g/kg) over 2 minutes. Beginning 20 minutes after the glucose bolus, tolbutamide was administered as a bolus of 300 mg (Orinase

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Submitted October 12, 2000; accepted December 31, 2001.

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0026-0495/02/5106-0002$35.00/0
doi:10.1053/meta.2002.32625

Table 1. Clinical Characterization of Patients With CPEO

Patient	Gender (M/F)	Age (yr)	BMI (kg/m^2)	Glucose Tolerance Status	HbA_{1c} (%)	CHOL (mg/dL)	TG (mg/dL)	Common Deletion	RRFs	Q10 Treatment	Family History for Diabetes	Clinical Signs and Symptoms	Age at Onset (yr)
HR	F	43	24.7	IGT	5.5	165	82	+	+	+	−	Ptosis, external ophthalmoplegia, limb weakness	21
HE	F	65	20.4	Diabetes	7.6	233	109	−	?	+	+	Ptosis, external ophthalmoplegia, pigmentary retinopathy, limb weakness, dysphagia, hypacusis	47
HOM	F	73	24.4	NGT	5.4	180	70	−	+	+	+	Ptosis, external ophthalmoplegia, limb weakness, hypacusis	52
JM	M	55	25.9	IGT	5.1	276	95	+	?	+	−	Ptosis, limb weakness	42
LE	F	69	37.9	NGT	5.6	220	169	+	+	+	−	Ptosis, external ophthalmoplegia, limb weakness,	5
SE	M	51	23.7	IGT	5.2	180	73	−	?	−	−	Ptosis, external ophthalmoplegia, pigmentary retinopathy, hypacusis, blurred speech	20

Abbreviations: CHOL, cholesterol; TG, triglycerides; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Diagnostic, UpJohn, Kalamazoo, MI). The patient HE with known diabetes received a bolus of human insulin of 0.01 U/kg instead (Normalinsulin H, Hoechst, Frankfurt, Germany). Samples for glucose and insulin determination were obtained at 1, 2, 3, 4, 5, 6, 8, 10, 15, 19, 22, 30, 40, 50, 70, 90, and 180 minutes after the end of the glucose injection.

Assays

Blood was centrifuged and glucose measured by the glucose oxidase method using a Beckman Glucose Analyzer 2 (Beckman Instruments, Fullerton, CA). The remaining plasma was stored at -20°C for later insulin determination with an enzyme-linked immunosorbent assay (Boehringer Mannheim, Mannheim, Germany). C-peptide was measured with a double-antibody, liquid phase radioimmunoassay (Biermann, Bad Nauheim, Germany). HbA_{1c} was analyzed by high-performance liquid chromatography (Diamat; Biorad, Hercules, CA).

ICA were assayed by classical immunofluorescence technique using fresh frozen sections of human pancreatic tissue. Insulin autoantibodies (IAA) were determined in a competitive, fluid-phase radiobinding assay. Lactate was measured with the Ectachem Clinical Chemistry Slides (LAC; Johnson and Johnson, New Brunswick, NJ). Creatinine was determined with the Jaffé kinetic method (Wako Chemicals, Neuss, Germany). Cholesterol was assayed with the CHOD-PAP method, triglycerides with the GPO-PAP method (Boehringer Mannheim).

Calculations

The $AIR_{Glucose}$ or first-phase insulin response represents insulin secretion and was calculated as the mean increment above the basal insulin values at 2, 3, 4, 5, 6, 8, and 10 minutes after glucose injection. Conard's coefficient of glucose assimilation (ie, glucose tolerance index Kg) was computed as the linear least square regression line to natural logarithm of the glucose concentration between 8 and 19 minutes after the glucose bolus and was used as an indicator for glucose tolerance status.[18,19] Insulin sensitivity index (SI) and glucose effectiveness (Sg) were calculated using a computerized program (MINMOD, copyright, Bergman et al[20]). SI estimates insulin sensitivity, whereas Sg represents the fractional glucose turnover at basal insulin.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 6.1.3 (SPSS, Chicago, IL).

For a description of demographic, anamnestic parameters, and results, median, minimum, and maximum were used because the data did not follow a normal distribution. Mann-Whitney *U* test was used to test whether there was a difference between patients and the matched-pair control group for glucose assimilation (Kg), insulin secretion ($AIR_{Glucose}$), insulin sensitivity (SI), fasting insulin, or glucose effectiveness (Sg). As CPEO is a rare disease, only a small number of 6 patients could be investigated. Statistical analysis has to be considered explorative.

RESULTS

Three of 5 patients with CPEO, but without known diabetes, showed an impaired glucose tolerance ($Kg < 1.1\% \cdot min^{-1}$) in the IVGTT. Table 2 shows the results of the minimal model analysis. One patient had overt diabetes mellitus for 5 years and had been treated with sulfonylurea (Glibenclamid, 5.25 mg/d). A family history of diabetes mellitus was positive in 2 patients (HE, HOM), 1 patient had known hypertension (JM). None of them had known hyperuricemia. In 3 patients, the common deletion could be detected in a muscle biopsy (HR, JM, and LE). Three patients (HR, HOM, and LE) showed the typical RRFs.

Fasting glucose was elevated in the diabetic patient, HE (133

Table 2. Results of Minimal Model Analysis

Patient	Fasting Glucose (mg/dL)	Fasting Insulin (pmol/L)	K_G Value (%/min^1)	SI*	Sg†	$AIR_{Glucose}$ (pmol/L)	C-Peptide (24-h urine) (μg/d)
HR	92	51.6	0.89	8.3	1.4	157.0	206.2
HE	133	59.4	0.69	1.0	1.3	9.1	—
HOM	86	37.2	2.26	10.2	2.2	282.1	—
JM	86	63.7	1.01	10.2	1.6	145.4	93.2
LE	114	168.3	2.26	2.1	1.4	814.2	1.9
SE	88	90.2	0.90	10.7	0.5	245.7	117.0
Patients‡	90	61.6	0.96	9.2	1.4	201.4	105.1
Controls‡	77	71.6	1.25	7.7	2.2	312.0	—
Patients§	86-133	37.2-168.3	0.69-2.26	1.0-10.7	0.5-2.2	9.1-814.2	1.9-206.2
Controls§	72-86	61.6-106.7	1.10-1.50	6.4-11.3	1.8-2.6	267.0-744.0	—

*SI · 10^{-5} min^{-1}/pmol/L; Sg · 10^{-2} min^{-1}; ‡median; §minimum and maximum.

mg/dL) and in patient LE (114 mg/dL) in whom the IVGTT did not show an impaired glucose tolerance (Kg = 2.26% · min^{-1}). Fasting plasma insulin was elevated in only 1 patient (LE). Low SI, which indicates insulin resistance, was seen in LE and HE. Insulin secretion estimated by first phase insulin ($AIR_{Glucose}$) and C-peptide excretion showed opposite results: first-phase insulin was slightly decreased in patient HR and JM, whereas C-peptide was normal in JM and even increased in HR. HE had very low $AIR_{Glucose}$, LE showed a very high $AIR_{Glucose}$. Glucose effectiveness (Sg) estimated by the minimal model was decreased for all patients except for HOM when compared with the matched-pair control group.

Testing for ICA was borderline positive (5 JDFu) only for LE. Lactate before and during IVGTT was normal in all patients. HbA_{1c} was elevated only in the diabetic patient, HE (7.6%). Hypercholesterinemia was detected in 3 patients, whereas triglycerides and serum creatinine were normal in all patients.

Statistical analysis showed a significant difference in age ($P < .001$) and BMI ($P = .02$) between patients and subjects in the control group, but not in gender ($P = .9$). Therefore, matched-pairs for gender, age, and BMI were selected for statistical analysis. There was no statistically significant difference now between the patients and the control group ($P = .69$ for age and $P = .94$ for BMI). The Mann-Whitney U test showed a significant difference only for glucose effectiveness Sg ($P = .016$). No influence of age or BMI could be shown on Sg, whereas age had an influence on SI ($P = .03$).

DISCUSSION

In contrast to a number of recent investigations about mitochondrial diabetes with the 3243 mutation, there are only few reports about diabetes mellitus in other mitochondrial diseases, eg, CPEO or KSS. There is evidence, however, that the incidence of diabetes mellitus in patients with CPEO or KSS is several times higher than in the normal population.[11,16] Three of our 6 patients with CPEO were shown to have IGT and 1 patient already had overt diabetes mellitus. Whether the 3 patients with IGT will develop diabetes within the next years remains to be seen, but this data confirms the impression that CPEO is frequently associated with a defect in glucose metabolism.

There were controversial findings about the underlying pathomechanisms in patients with mitochondrial diabetes with the 3243 mutation: a defect in insulin secretion was seen in some patients,[4-6] insulin resistance was predominant in others,[7,21] In patients with CPEO or KSS, however, very few reports are available. Piccolo et al[22] demonstrated normal insulin receptor parameters and low insulin secretion in 1 diabetic patient with KSS. In 1988, Tanabe et al[23] reported a patient with KSS and diabetes in whom the euglycemic glucose clamp technique demonstrated normal insulin sensitivity, but an intravenous glucagon tolerance test showed impaired insulin secretion. Others reported diabetic patients with CPEO or KSS and low insulin secretion, but no investigations of insulin sensitivity had been performed.[11,24,25]

In the present study, 6 patients with CPEO were investigated using an IVGTT with minimal model analysis. As no difference for insulin sensitivity (SI) and insulin secretion ($AIR_{Glucose}$) could be demonstrated between patients and controls, impaired glucose effectiveness (Sg) seems to be responsible for IGT in 3 of our 6 CPEO patients. Sg describes the effect of glucose per se on glucose metabolism, independent from an increase in insulin above basal.[26] In the basal state, glucose-mediated glucose uptake primarily affects such insulin-insensitive tissues as the central nervous system (CNS), splanchnic bed, and blood cells. During hyperglycemia, however, insulin-independent, as well as insulin-dependent glucose uptake, occurs in skeletal muscle.[27,28]

Impaired glucose effectiveness has been described in patients with type 2 diabetes, as well as with IGT.[28-30] Del Prato et al[28] suggested the existence of "glucose resistance" if the mass action of glucose in the hyperglycemic state is reduced. Nielsen et al[31] found a normal hepatic response to glucose in patients with type 2 diabetes, ie, a progressive and comparable decrease in endogenous glucose production and total glucose output in subjects with and without diabetes mellitus. The ability of glucose to stimulate its own uptake, however, was impaired in the subjects with overt diabetes.[31] Therefore, impaired glucose effectiveness in diabetes or IGT seems to be due to a defect in skeletal muscle in the presence of normal hepatic response.

In our CPEO patients, Sg was decreased when compared with the control subjects. Minimal model-derived glucose ef-

fectiveness (when using the above-mentioned protocol) cannot differentiate between hepatic and/or muscle involvement. Therefore, further studies in our CPEO patients would be necessary to determine whether impaired glucose effectiveness is due to a defect in glucose uptake, an impaired suppression of endogenous glucose production, or a combination of both. As our patients showed symptoms of muscle weakness, one might speculate about an involvement of skeletal muscle in glucose metabolism as well. In this case, low Sg would be due to impaired glucose disposal rather than a defect in hepatic response. We can only speculate about the mechanisms leading to impaired glucose effectiveness in our CPEO patients. If it is indeed due to a defect in glucose disposal, glucose uptake might be the limiting step, eg, impaired due to a defect or decreased number of glucose transporters. A second explanation might affect glucose phosphorylation or glycogen synthesis. To our knowledge, this is the first report about impaired glucose effectiveness in patients with CPEO.

$AIR_{Glucose}$ of patients HR and JM was in the lower normal range. Although their insulin secretion can still be considered normal under normal conditions, it cannot be ruled out that their insulin secretion is also impaired relative to the impaired glucose effectiveness. In this case, a secretion defect or at least the impossibility to compensate for low Sg with an increase in $AIR_{Glucose}$ would contribute to the development of IGT in CPEO.

Considering the diabetic patient HE, she showed a normal fasting insulin, but a low SI indicating insulin resistance. In addition, $AIR_{Glucose}$ and Sg were impaired. Therefore, diabetes in CPEO might be a combination of a defect of glucose effectiveness, impaired insulin secretion, as well as insulin resistance. Since we have investigated only 1 patient with CPEO and diabetes mellitus, however, this might be incidental.

There is no specific treatment available for patients with mitochondrial diseases so far. Besides a symptomatic therapy, treatment with ubiquinone (coenzyme Q10) is the only approach. There is some evidence that ubiquinone has a beneficial effect on the clinical manifestations of a number of mitochondrial diseases, such as muscle strength, lactacidemia, cerebellar symptoms, or cardiac conduction disturbances.[15,32,33] Except for patient SE, all patients were treated with ubiquinone (Q10) for at least 6 months. These findings might explain the normal lactate in the present study. Whether Q10 has a beneficial effect on glucose tolerance and influenced the results in our patients remains open.

In conclusion, there is a high incidence of IGT or overt diabetes mellitus in patients with CPEO. Impaired glucose effectiveness seems to play a major role. An insulin secretion defect, as well as insulin resistance, contribute to the development of overt diabetes so that diabetes in patients with CPEO seems to be multifactorial. Whether the pathomechanisms of mitochondrial diabetes are the same in patients with the 3243 mutation and in patients with CPEO remains to be seen.

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