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Posttreatment Neuropathy in Diabetic Subjects With Mitochondrial tRNA (Leu) Mutation

Painful sensation and/or paresthesia are sometimes precipitated by the institution of insulin treatment or strict glycemic control. The phenomena is generally called "posttreatment neuropathy," which is regarded as an entity of diabetic neuropathy. Its cause and individual predisposition are unknown, and the prevalence is generally thought to be low (1,2).

We came across five diabetic patients with posttreatment neuropathy (Table 1). They noticed that pain or paresthesia in legs developed or deteriorated several weeks after initiation of insulin therapy. In cases 1 and 3, the pain was so severe that they became depressed and needed adequate pharmacotherapy. All five patients were thereafter identified as having a mitochondrial tRNA (Leu) mutation at position 3243 (3,4).

Considering that diabetes associated with this mitochondrial mutation is relatively uncommon, it is surprising that these cases of posttreatment neuropathy occurred in five of seven insulin-treated patients with this mitochondrial mutation whom we have identified in Saiseikai Central Hospital. It appears unlikely that the posttreatment neuropathy coincided fortuitously in these patients, considering the high occurrence of these episodes with this type of seemingly uncommon mitochondrial tRNA (Leu) mutation.

A possible explanation may be related to the following three mechanisms: *1*) the patients with mitochondrial mutation have a possible impairment of ATP production for maintaining normal nerve function and of antioxidant capacity to oxygen radicals; 2) long-term hyperglycemia can induce fragmentation of Cu, Zn-SOD, a radical-scavenging enzyme (5); and 3) improved metabolic control may change the oxygen affinity of the erythrocytes that brings about rapid improvement in tissue oxygenation (6,7).

Therefore, we speculated that the oxygen utilization triggered by change of metabolic control may jeopardize already impaired nerve tissues of diabetic patients with mitochondrial dysfunction to oxidative damages (8).

Although the detailed mechanisms are unknown, we wish to emphasize the importance of checking up on the mitochondrial tRNA (Leu) mutation in

Table 1—*Clinical features of five diabetic patients with posttreatment neuropathy of leg pain or paresthesia*

Case No.	1	2	3	4	5
Sex (M/F)	F	M	M	M	F
Age of diagnosis of diabetes (years)	31	38	44	42	47
Age at start of insulin (years)	31	38	44	46	57
Changing feature of FPG (mM)	14.7→10.5	10.0→7.7	9.4→6.8	17.9→8.6	14.5→6.4
Changing feature of HbA_{1c} (%)	11.9→9.2	11.5→10.2	14.9→6.4	15.8→7.8	12.7→9.7
Characteristics of pain or paresthesia in leg	Severe pain and paresthesia	Mild paresthesia	Severe pain and paresthesia	Mild paresthesia	Mild pain and paresthesia
Onset time of symptoms after start of insulin therapy	4 weeks	2 weeks	4 weeks	14 weeks	4 weeks
Duration of the worsening of symptoms	2 years	1 month	1 year	3 months	1 year
Mitochondrial tRNA (Leu) mutation at position 3243 in leucocyte	+	+	+	+	+

Posttreatment neuropathy of leg pain or paresthesia occurred or deteriorated after glycemic control by insulin therapy. All of the patients were documented to have mitochondrial tRNA (Leu) mutation at position 3243 in leucocyte. FPG, fasting plasma glucose level. Changing features of FPG and HbA_{1c} indicate the change of 2 or 3 months after the start of insulin treatment. The pain and the paresthesia were symptoms that the patients suffered after initiation of insulin therapy, and all the syptoms were determined by clinical questioning. Severe pain indicates the intense pain with which the patients could not endure without receiving some pharmacotherapy. The frequency of patients with this mitochondrial mutation is expected to be ~2% in the population of non-insulin-dependent diabetic subjects with a family history of diabetes (4). On the other hand, this mutation was not found in 200 subjects with normal glucose tolerance and no family history of diabetes (4).

diabetic patients, and a greater caution should be paid in correcting hyperglycemia rapidly in patients with the mutation.

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Insulin Resistance in Mitochondrial Gene Mutation

An association with diabetes has been reported in some patients with a mitochondrial gene mutation (1,2). Because mitochondrial oxidative phosphorylation is important in the glucose-induced secretion of insulin by pancreatic β-cells, a mitochondrial gene mutation may produce diabetes because of an insufficient secretion of endogeneous insulin. However, the insulin sensitivity of patients with mitochondrial gene mutation has not yet been determined in the peripheral tissues. Accordingly, we examined the insulin sensitivity in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episode (MELAS).

In April 1993, a 41-year-old Japanese woman was admitted to our hospital with tonic-clonic convulsions. She had suffered from diabetes for 3 years; it was poorly controlled, despite dietary treatment and the administration of an oral hypoglycemic agent. On admission, she showed a high level of plasma glucose (22 mM), HbA_{1c} (10.9%), and serum lactate (3.5 mM). She exhibited a mild hearing disturbance and a muscle biopsy showed ragged-red fibers. Tests for islet cell antibody and insulin receptor antibody were negative. The region encoding $tRNA^{Leu(UUR)}$ in the mitochondrial DNA isolated from peripheral leukocytes was amplified by polymerase chain reaction (PCR). PCR products were digested with *Apa* I, and subjected to agarose-gel electrophoresis (3). We identified an A to G transition at nucleotide 3,243 in the $tRNA^{Leu(UUR)}$ gene. Thus, a diagnosis of MELAS was made.

In September 1993, after the hyperglycemia had been corrected by insulin treatment (plasma glucose, 9 mM; HbA_{1c}, 6.7%), we conducted the following studies: Tests for serum C-peptide immunoreactivity to the oral administration of glucose showed an impaired endogeneous insulin secretory capacity. The metabolic clearance rate of glucose (MCR), estimated by the euglycemic hyperinsulinemic glucose clamp technique (4), was lower in our patient (5.73 mg · kg^{-1} · min^{-1}) compared with the MCR of nondiabetic control subjects (9.37 ± 0.92, $n = 5$; mean ± SD). Because hepatic gluconeogenesis is enhanced via the Cori cycle activated by the hyperlactatemia in MELAS, the MCR in our patient may have been underestimated. However, the level of plasma insulin (600 pM) in the glucose clamp study was elevated sufficiently to suppress the production of hepatic glucose. Our finding indicated the presence of insulin resistance in this patient with MELAS. An earlier study (5) had shown no insulin resistance in a patient with Kearns-Sayre syndrome, which is one of the mitochondrial myopathy. The authors concluded that diabetes in that patient was caused by an insufficient secretion of insulin.

In our patient with MELAS, a metabolic dysfunction of the muscle may have been involved in causing insulin resistance because muscle tissue is an important target for insulin. In addition, the glucose toxicity induced by prolonged hyperglycemia may have reduced the rate