Liver and Kidney Function in Japanese Patients With Maturity-Onset Diabetes of the Young

NAOKO IWASAKI, MD
MAKIKO OGATA, MD
OSAMU TOMONAGA, MD
HIROYUKI KUROKI, MD
TADASU KASAHARA, MD
NOBUKI YANO, MD
YASUHIKO IWAMOTO, MD

OBJECTIVE — Heterozygous mutations in the transcription factors hepatocyte nuclear factor (HNF)-1α, HNF-1β, and HNF-4α are associated with maturity-onset diabetes of the young (MODY) and are believed to cause this form of diabetes by impairing pancreatic β-cell function. The HNFs also play a central role in the tissue-specific regulation of gene expression in liver and kidney, suggesting that patients with MODY due to a mutation in HNF-1α, HNF-1β, or HNF-4α may exhibit abnormal liver or kidney function. Here, we have examined liver and kidney function in a series of Japanese patients with HNF-4α/MODY1, HNF-1α/MODY3, and HNF-1β/MODY5 diabetes.

RESEARCH DESIGN AND METHODS — Clinical and biochemical data were obtained from Japanese subjects with HNF-1α, HNF-1β, and HNF-4α diabetes. The clinical data included information on BMI, age at diagnosis, current treatment, and the presence and nature of any complications. The biochemical studies examined liver and kidney function and included measures of alanine and aspartate aminotransferase, γ-glutamyl transpeptidase, blood urea nitrogen, creatinine, uric acid, total and HDL cholesterol, triglycerides, and 17 serum proteins.

RESULTS — The present age and duration of diabetes were similar in patients with HNF-1α, HNF-1β, or HNF-4α diabetes, as was the age at diagnosis of diabetes in the youngest generation. All subjects were lean. Of the subjects with HNF-1α and HNF-4α diabetes, 50% were treated with insulin, as were all three subjects with HNF-1β diabetes. Retinopathy was present in patients with each form of diabetes. None of the subjects with HNF-4α diabetes had evidence of nephropathy, whereas 36% of the patients with HNF-1α diabetes and 100% of those with HNF-1β diabetes showed diminished kidney function. The three subjects with HNF-1β diabetes also had abnormally high serum creatinine, uric acid, and blood urea nitrogen levels, which are consistent with impaired kidney function, and one of seven subjects with HNF-1α diabetes had a mild elevation in creatinine and blood urea nitrogen levels. These values were within the normal range in the three patients with HNF-4α diabetes. Although the HNFs play a role in regulating the expression of the genes for most, if not all, serum proteins, there was no decrease in the levels of any of the 17 serum proteins examined, and most were within or slightly above the normal range. Lipoprotein(a) [Lp(a)] levels were elevated in the three patients with HNF-4α diabetes and in one patient with HNF-1β diabetes, and in a second patient with HNF-1β diabetes, Lp(a) was at the upper limit of normal.

CONCLUSIONS — The results indicate that as in white patients, MODY resulting from mutations in the HNF-1α, HNF-1β, and HNF-4α genes in Japanese patients may be a severe disease similar to classic type 2 diabetes. In addition, they suggest that patients with HNF-1β diabetes may be characterized by diminished kidney function and perhaps abnormal liver function. Further studies are needed to determine whether tests of liver and kidney function will be useful in the diagnosis and subclassification of MODY.

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From the Diabetes Center (N.I., M.O., O.T., Y.I.), Tokyo Women's Medical University; Zyousai Hospital (H.K., T.K.), Tokyo; and Heiwadai Naika Hospital (N.Y.), Miyazaki, Japan.

Address correspondence and reprint requests to Naoko Iwasaki, MD, Diabetes Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.

Abbreviations: ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase; GTP, glutamyl transpeptidase; HNF, hepatocyte nuclear factor; IPF, insulin promoter factor; Lp(a), lipoprotein(a); MODY, maturity-onset diabetes of the young.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Maturity-onset diabetes of the young (MODY) is a group of diseases characterized by autosomal dominant inheritance, onset of nonketotic diabetes usually before 25 years of age, and deficient insulin secretory response to glucose (1). MODY can result from heterozygous mutations in the glycolytic enzyme glucokinase/MODY2 (2) as well as in four different transcription factors—hepatocyte nuclear factor (HNF)-4α/MODY1 (3), HNF-1α/MODY3 (4), insulin promoter factor (IPF)-1/MODY4 (5), and HNF-1β/MODY5 (6). In addition, patients with mutations in the insulin gene (7) exhibit many of the features of MODY and perhaps familial hyperinsulinemia or hyperproinsulinemia should be regarded as a subtype of MODY. Clinical studies have shown that mutations in these genes are associated with abnormal pancreatic β-cell function (1,2,8–10), indicating that MODY is a primary genetic disorder of the β-cell. However, with the exception of the insulin gene—whose expression is limited to the β-cell in adults—glucokinase, the HNFs, and IPF-1 are expressed in other tissues, suggesting that mutations in these genes may have diverse physiological consequences. This expectation has been confirmed in clinical studies of patients with glucokinase diabetes, the results of which have shown that the mild hyperglycemia that characterizes this form of diabetes results from abnormalities of glucose metabolism in the β-cell and liver, the two tissues in which glucokinase is expressed at highest levels. The deficiency of glucokinase leads to a resetting (i.e., a rightward shift) of the glucose sensitivity of the β-cell, and to decreased glycogenesis and increased gluconeogenesis in the liver after a meal (10,11). The identification of extrapancreatic abnormalities in patients with MODY might provide surrogate markers that could be used for the diagnosis and subclassification of this disorder.

The liver-enriched transcription factors HNF-1α, HNF-1β, and HNF-4α were first identified through studies of transcription factors that play a role in the tissue-specific regulation of gene expression in the liver

(12,13). The characterization of these transcription factors showed that they were liver-enriched but not liver-restricted, and that they were present at variable levels in other tissues, including kidney and intestine. The observation that mutations in these three liver-enriched transcription factors were associated with MODY was a surprising discovery, especially because these proteins were not known to play a significant role in regulating gene expression in the pancreatic β-cell and because there were no readily apparent abnormalities in liver, kidney, or intestinal function in patients with mutations in these genes (3,4). However, subsequent studies have revealed defects in other tissues. Patients with HNF-4α diabetes exhibit abnormal α-cell function, which implies that this form of diabetes may be characterized by defective function in more than one type of pancreatic islet cell (14). HNF-4α diabetes may also be associated with elevated serum lipoprotein(a) [Lp(a)] levels (15). Patients with HNF-1α diabetes may exhibit a reduction in the renal threshold for glucose, resulting in glycosuria, in the presence of normal blood glucose levels, which suggests that kidney function may also be abnormal in this form of diabetes (16). Finally, mice completely lacking HNF-1α have profound liver dysfunction as well as proximal renal tubular dysfunction, including phenylketonuria and massive glycosuria (17).

To gain a better understanding of the physiological consequences of HNF-1α, HNF-1β, and HNF-4α mutations, we have examined the clinical and biochemical features, including liver and kidney function, of groups of Japanese subjects with MODY due to mutations in each of these genes.

RESEARCH DESIGN AND METHODS

Subjects

The study population consisted of members of nine unrelated Japanese families with MODY due to mutations in the HNF-1α gene (seven families) (18), HNF-1β gene (one family) (6), and HNF-4α gene (one family) (19). The families and family members with HNF-1α diabetes studied include J2-10 (mutation K205Q, subjects II-1, II-2, and I-2); J2-15 (mutation P379fsdelCT, subjects III-1 and III-3); J2-22 (mutation L584S585fsinsTC, proband); J2-41 (mutation R263C, proband); J2-86 (mutation T392fsdelA, proband); J2-91 (mutation R131Q, proband); and J2-105 (mutation L12H, subjects II-2, and III-1) (18). The MODY family with HNF-1β diabetes studied was J2-20 (mutation R177X, subjects II-9, III-2, and III-3) (5), and the family with HNF-4α diabetes was J2-21 (mutation R127W; subjects I-5, II-1, III-4, and IV-2) (19). Informed consent was obtained from each subject before the study.

Clinical and biochemical studies

The following information was obtained from each subject: present age, age at diagnosis of diabetes, duration of diabetes, BMI, maximum BMI, current treatment, and nature and severity of any complications. A blood sample was taken for measurement of total serum protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GTP), blood urea nitrogen, creatinine, uric acid, total and HDL cholesterol, and triglycerides. A fasting blood sample for determination of specific serum protein levels (albumin; antithrombin III; apolipoproteins A1, A2, B, C2, C3, and E; α_1-acid glycoprotein; α_1-antitrypsin; ceruloplasmin; complement C3; fibrinogen; hemopexin; Lp(a); prothrombin; and transferrin) was obtained from a subset of the subjects described above: family J2-10, subjects II-1, II-2, and I-2; J2-86, proband; J2-91, proband; J2-105, subjects III-1 and II-2; J2-20, subjects II-9, III-2, and III-3; and J2-21, subjects II-1, III-4, and IV-2. The diagnosis of diabetic retinopathy was made by an ophthalmologist in the Diabetes Center. Diabetic nephropathy was diagnosed if persistent proteinuria was present (i.e., proteinuria exceeded 0.5 g/day or >300 mg/dl), and subjects were defined as having chronic renal failure if the serum creatinine levels exceeded 177 μmol/l. Antithrombin III was measured by the synthesized substrate method; apolipoproteins A1, A2, B, C2, C3, E, and Lp(a), complement C3, and transferrin by turbidimetric immunoassay; α_1-acid glycoprotein, α_1-antitrypsin, hemopexin, and ceruloplasmin by nephelometry; fibrinogen by light scattering; and prothrombin by chromorphic prothrombin time (Mitsubishi Biochemical, Tokyo). Group differences were assessed by analysis of variance (ANOVA) and were considered significant if $P < 0.05$.

RESULTS

Clinical studies

The clinical features of the three groups of MODY patients are summarized in Table 1. The mean age at diagnosis was similar for patients with HNF-1α and HNF-1β diabetes and was higher for those with HNF-4α diabetes. However, this difference was due to the fact that one of the four subjects with HNF-4α diabetes was diagnosed at 90 years of age. The age at diagnosis of the other two subjects with HNF-4α diabetes was 38 and 17 years, and a 12-year-old subject with the R127W mutation in HNF-4α does not yet have diabetes. The subjects with different forms of HNF diabetes were relatively lean, and there was no significance difference in mean BMI among the three groups. Of the 18 MODY patients, 11 were currently being treated with insulin, including 2 of 4 and 6 of 11 subjects with HNF-4α and HNF-1α diabetes, respectively, and all 3 subjects with HNF-1β diabetes. Retinopathy was a common complication associated with HNF-4α, HNF-1α, and HNF-1β diabetes, with 2 of 4, 5 of 11, and 3 of 3 patients, respectively, having simple or proliferative retinopathy. However, there was variability in the incidence and severity of nephropathy among the three groups of subjects. There was no evidence of nephropathy in the four patients with HNF-4α diabetes. Among the 11 patients with HNF-1α diabetes, 7 had no evidence of nephropathy, 3 had persistent proteinuria, and 1 had chronic renal failure. Evidence of renal dysfunction was exhibited by all three HNF-1β diabetes patients, including one patient with persistent proteinuria and two patients with chronic renal failure, one of whom subsequently underwent a successful kidney transplant.

The total serum protein levels were similar in the three groups of patients as were cholesterol (total and HDL) and triglyceride levels (Table 1). Biochemical tests of kidney function (blood urea nitrogen, serum creatinine, and uric acid) and liver function (ALT, AST, and γ-GTP) were within normal levels or just above the upper limit of normal for the three subjects with HNF-4α diabetes and for the seven subjects with HNF-1α diabetes. By contrast, the blood urea nitrogen, creatinine, and uric acid levels were at the upper limit of normal or exceeded normal values in the subjects with HNF-1β diabetes, which is consistent with the presence of severe nephropathy in this group. AST, ALT, and γ-GTP levels were also significantly higher in the group of patients with HNF-1β diabetes.

The abnormal kidney and liver function test results in the patients with HNF-1β diabetes led us to reexamine the clinical records of these three subjects to search for other

Table 1— *Clinical features of Japanese patients with HNF-4α, HNF-1α, and HNF-1β diabetes*

Parameter	HNF-4α	HNF-1α	HNF-1β	Reference values
n (M/W)	4 (2/2)	11 (6/5)	3 (1/2)	
Present age (years)	54.2 ± 10.6	34.3 ± 3.9	44.7 ± 11.3	—
Age at diagnosis (years)	48.3 ± 21.6	16.1 ± 2.0	21.7 ± 9.3	—
Duration (years)	20.3 ± 8.9	17.7 ± 2.5	25.0 ± 1.5	—
BMI	21.8 ± 1.4	20.6 ± 0.4	19.7 ± 1.9	—
Maximum BMI	23.9 ± 1.6	22.3 ± 0.9	23.3 ± 2.1	—
Total serum protein (g/l)	69 ± 4	73 ± 1	71 ± 0.2	65–82
ALT (IU/l)	14.3 ± 2.3	17.2 ± 1.8	50.0 ± 29.7*	4–31
AST (IU/l)	20.3 ± 4.1	18.7 ± 1.4	51.0 ± 24.8*	11–31
γ-GTP (IU/l)	13.3 ± 5.0	13.5 ± 4.0	164.7 ± 133.2*	Male, 8–77; female 7–28
Blood urea nitrogen (nmol/l)	5.5 ± 0.7	6.0 ± 0.5	19.2 ± 8.5*	2.9–7.1
Serum creatinine (μmol/l)	63.6 ± 11.5	81.3 ± 8.8	380.1 ± 238.7*	62.0–115.0
Uric acid (μmol/l)	321 ± 30	238 ± 24	488 ± 30*	Male, 220–410; female,143–351
Total cholesterol (mmol/l)	5.33 ± 0.91	5.12 ± 0.18	5.35 ± 0.34	3.10–5.69
HDL cholesterol (mmol/l)	1.85 ± 0.70	1.84 ± 0.11	1.77 ± 0.40	Male, 1.09–1.71; female, 1.30–1.86
Triglycerides (mmol/l)	1.17 ± 0.3	0.93 ± 0.1	1.17 ± 0.3	0.45–1.69
Treatment (diet/oral hypoglycemic agent/insulin)	2/0/2	2/3/6	0/0/3	
Retinopathy (not determined/absent/ simple/proliferative)	1/1/0/2	0/6/0/5	0/1/0/2	
Nephropathy (absent/persistent proteinuria/chronic renal failure)	4/0/0	7/3/1	0/1/2	

Data are means ± SEM or *n*. ANOVA was used for statistical analysis. *$P < 0.05$ compared with HNF-4α and HNF-1α.

possible explanations for these results. Subject III-3 (6), a 33-year-old man, was diagnosed as having type 2 diabetes at 15 years of age, and persistent proteinuria was evident at 18 years of age. Hyperbilirubinemia, elevated ALT and AST levels, and abnormal hepaplastin test were observed when the patient was 19 years old. Ultrasonography revealed liver fibrosis. Hepatitis and alcohol- and drug-induced disease were excluded, and the source of the liver dysfunction was classified as unknown. The patient's most recent examination in 1997, at 32 years of age, showed that ALT, AST, and γ-GTP levels were still elevated (93, 145, and 489 IU/l, respectively). At 24 years of age, creatinine clearance was lower than normal (50–60 ml/min [normal, 100]), and urine protein was 0.4 g/day, and although there was evidence of nephropathy, there was no diabetic retinopathy. Ultrasonography at this time showed that both kidneys were reduced in size (right, 86 × 36 mm; left, 92 × 42 mm [normal range, 100–120 for the first measurement and 40–50 for the second measurement]). The echo level of the cortex of both kidneys was also high, which is a common feature of kidney dysfunction. There were four cysts in the right kidney and one cyst in the left. Simple retinopathy was first observed in 1998, when the patient was 33 years old; his serum creatinine levels remain elevated at 126 μmol/l. His older sister (subject III-2) was diagnosed with type 2 diabetes at 10 years of age. It was noted that at 23 years of age, she had proliferative retinopathy, and her serum creatinine level was 124 μmol/l. Renal ultrasonography revealed a high echo level in the cortex, but no renal cysts were evident. At 24 years of age, her serum creatinine level had increased to 133 μmol/l, and urine protein was 0.2 g/day. Dialysis treatment was started at 31 years of age, and she received a kidney transplant at 32 years of age (there was no renal biopsy, and it is unknown whether the nephropathy was a consequence of the diabetes or due to a direct effect of the HNF-1β mutation on kidney development or function). Her liver function test results have been consistently normal.

The affected mother (subject II-9) was diagnosed with diabetes at 40 years of age. Renal insufficiency with proteinuria and proliferative retinopathy was noted at 55 years of age. She is currently 67 years of age and her serum creatinine level is 186 μmol/l and she has evidence of liver dysfunction: 49, 36, and 52 IU/l for AST, ALT, and γ-GTP, respectively. The father, who has two normal HNF-1β alleles, developed typical type 2 diabetes at 50 years of age. He has had diabetes for 22 years and shows evidence of background retinopathy but no kidney or liver dysfunction.

Biochemical studies

The HNFs play a key role in the regulation of expression of many serum proteins, including albumin, the apolipoproteins, and the clotting factors (12). There were no significant differences in the levels of 17 different serum proteins among the three groups of MODY patients except for a slight elevation in Lp(a) in the three patients with HNF-4α diabetes (Table 2). Lp(a) was also elevated in one patient with HNF-1β diabetes and was at the upper limit of normal in a second patient, and the mean level in this group was significantly higher than that of the HNF-1α group. Otherwise, the levels of the various proteins were within the normal range or just above the upper limit of normal.

CONCLUSIONS — In 1965, Fajans and Conn (20) described a familial form of diabetes, which they called "maturity-onset type diabetes of young people," subsequently abbreviated to MODY. The studies of Fajans (1) and his collaborators as well as others suggested that MODY itself was likely to be a heterogeneous disorder, and

Table 2— *Serum protein levels of Japanese patients with HNF-4α, HNF-1α, and HNF-1β diabetes*

Protein	HNF-4α	HNF-1α	HNF-1β	Reference values
n (M/W)	3 (1/2)	7 (3/4)	3 (1/2)	
Albumin (g/dl)	3.9 ± 0.4	4.3 ± 0.1	4.2 ± 0.1	3.8–5.1
Antithrombin III	28.0 ± 0.4	27.7 ± 0.9	29.6 ± 1.8	21.0–34.0
Apolipoprotein A1	130.7 ± 25.7	153.6 ± 5.8	159.3 ± 4.7	98.0–180.6
Apolipoprotein A2	22.4 ± 2.8	33.9 ± 1.6	26.7 ± 5.4	22.0–44.0
Apolipoprotein B	101.3 ± 17.3	77.2 ± 6.2	105.7 ± 7.4	51.0–111.0
Apolipoprotein C2	5.03 ± 0.8	4.1 ± 0.5	5.3 ± 0.9	1.2–4.9
Apolipoprotein C3	13.0 ± 3.9	11.3 ± 1.5	17.0 ± 2.5	3.9–12.3
Apolipoprotein E	4.9 ± 1.3	5.8 ± 0.6	5.6 ± 0.7	2.4–6.3
α_1-acid glycoprotein	70.4 ± 8.0	58.5 ± 5.4	67.9 ± 5.2	32.0–98.0
α_1-antitrypsin	204.3 ± 4.3	216.6 ± 12.9	209.0 ± 20.6	170.0–310.0
Ceruloplasmin	29.1 ± 2.7	27.4 ± 1.8	25.9 ± 3.4	21.0–33.0
C3	66.0 ± 9.1	62.3 ± 3.7	62.3 ± 12.4	50.0–110.0
Fibrinogen	312.7 ± 31.0	266.8 ± 12.6	301.7 ± 29.4	155.0–415.0
Hemopexin	111.0 ± 4.7	81.4 ± 3.0	89.0 ± 12.1	50.0–110.0
Lp(a)	37.5 ± 2.5*	4.9 ± 0.8	23.9 ± 8.3	<30
Prothrombin	101.7 ± 4.7	111.0 ± 8.9	110.7 ± 8.4	80.0–110.0
Transferrin	272.7 ± 49.6	281.4 ± 18.6	246.0 ± 15.0	210.0–390.0

Data are means ± SEM, expressed in milligrams per deciliter unless otherwise indicated. *$P < 0.05$ compared with HNF-1α and HNF-1β by ANOVA.

molecular genetic studies have confirmed that this is indeed the case (2–6,21). These studies have shown that MODY can result from heterozygous mutations in at least five different genes—glucokinase, HNF-1α, HNF-1β, HNF-4α, and IPF-1.

Increasing awareness of MODY suggests that it is more common than previously thought, affecting 2–5% of all diabetic patients (1–3,22). In addition, MODY can masquerade as type 1 or type 2 diabetes (18,23), thereby contributing to misclassification. Although MODY is a primary genetic disorder of the pancreatic β-cell, the mutant genes associated with this disorder may be and often are expressed in other tissues. This is especially true of the liver-enriched transcription factors, HNF-1α, HNF-1β, and HNF-4α, which are expressed at high levels in pancreatic β-cell, liver, kidney, and intestine, and at lower levels in several other tissues (12,13). The function of these proteins in the regulation of gene expression in the liver has been extensively studied, and they act together and in combination with other liver-enriched transcription factors to stimulate cell-specific transcription in this tissue (12). They are responsible for regulating the expression of most serum proteins and liver enzymes involved in carbohydrate, lipid, and urea metabolism and detoxification (12,13,24). In the kidney, HNF-1α regulates the expression of the transporters involved in the reabsorption of glucose and phosphate from the forming urine (17).

We have compared the clinical and biochemical features of Japanese patients with different forms of MODY to determine whether there were features that might serve as surrogate markers to be used in subclassification and diagnosis. We found no clinical or biochemical features that would assist in the diagnosis of HNF-1α diabetes, nor did we find clinical features that distinguished HNF-4α diabetes. We observed, however, that Lp(a) levels were elevated in our small group of patients with HNF-4α diabetes, which was consistent with the observation of Lindner et al. (15), who showed a significant elevation of Lp(a) levels in a German family with a nonsense mutation (R154X) in HNF-4α. The clinical and biochemical studies of the family with HNF-1β diabetes in our study revealed several unusual features, including prominent kidney dysfunction in all of the subjects and liver dysfunction in two of three subjects.

Hyperlipidemia occurs frequently in patients with type 2 diabetes and is a component of the metabolic syndrome (25). The triglyceride levels were within normal limits in the 18 Japanese patients with MODY participating in our study, suggesting that syndrome X is not a feature of HNF diabetes.

In summary, the results demonstrate that MODY resulting from mutations in the HNFs is a severe form of diabetes in Japanese patients, as in subjects of European ancestry, that it often requires insulin treatment, and that it is associated with retinopathy and nephropathy (1,26,27). Kidney dysfunction appears to be a prominent feature of HNF-1β diabetes and subjects with this form of diabetes may be recognized by the coexistence of MODY and severe kidney disease (6,28). Liver dysfunction may also be a feature of HNF-1β diabetes. Further studies are needed to determine whether tests of liver and kidney function will be useful in the diagnosis and subclassification of MODY.

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