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Enlarged nephrons and severe nondiabetic nephropathy in hepatocyte nuclear factor-1β (HNF-1β) mutation carriers

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Enlarged nephrons and severe nondiabetic nephropathy in hepatocyte nuclear factor-1β (HNF-1β) mutation carriers.

Background. Mutations in hepatocyte nuclear factor-1β (HNF-1β) lead to a syndrome with diabetes and urogenital malformations [maturity onset of diabetes of the young, type 5 (MODY5)]. The aim of this study was to perform a clinicopathologic investigation of the renal disease in members of a Norwegian family with the HNF-1β mutation R137-K161del.

Methods. The study was based on long-term clinical observations of five mutation carriers, combined with renal biopsies from four of these. The biopsies were examined by light microscopy, immunohistochemistry, and transmission electron microscopy. The diameter of the glomerulus, proximal and distal tubules, in addition to thickness of the glomerular basement membrane (GBM), were measured in light microscopic slides and transmission electron micrographs. The results were compared with biopsies from adult patients with diabetic glomerulopathy, glomerulonephritis, and/or benign nephrosclerosis, and children with minimal-change glomerulopathy or glomerulonephritis, respectively.

Results. Clinically, there was a wide intrafamilial variation from stable or slightly increasing serum creatinine to progressive renal failure and end-stage renal disease (ESRD). In all cases, the kidney disease was diagnosed prior to diabetes. Hypertrophy of the proximal and distal tubules as well as enlarged glomeruli were found in three of four mutation carriers. Essentially normal nephrons were found in the 10-year-old boy. The thickness of the GBM was considered near normal in all mutation carriers. Oligomeganephronia was found in one patient.

Conclusion. Histopathologic and morphometric studies of kidney biopsies from four carriers of an HNF-1β mutation revealed enlarged glomeruli and tubular structures. Long-term clinical follow-up demonstrated that the renal disease developed prior to and independently of diabetes. Finally, there is a wide phenotypic variation of the renal disease caused by HNF-1β mutations.

Key words: hepatocyte nuclear factor-1β (HNF-1β), maturity onset diabetes of the young (MODY), hereditary nephropathy, diabetic glomerulopathy, oligomeganephronia.

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Mutations in hepatocyte nuclear factor-1β (HNF-1β) are associated with a syndrome characterized by diabetes, severe renal disease, and genital malformations [1–4]. This syndrome (MIM # 604284) referred to as maturity onset diabetes of the young (MODY) type 5, also known as the renal cysts and diabetes syndrome, involves kidneys, endocrine pancreas, genital system [4–6], hepatic function [7], and possibly the central nervous system [8]. The nephropathy is the most serious part of the syndrome, in some cases leading to kidney failure and transplantation.

HNF-1β, which is a nuclear protein essential in formation and differentiation of several organs, appears in the metanephros during early embryonal development [9–11]. Functional changes of the protein potentially cause developmental disorders in several organs. However, the nature of the hereditary nephropathy associated with HNF-1β mutations is not well understood. A few histopathologic investigations based on renal biopsies have resulted in diagnoses such as oligomeganephronia [4, 12], cystic dysplasia [6], and hypoplastic glomerulocystic kidney disease [13, 14]. Absence of normal nephrogenesis was observed in a 17-week-old fetus [15].

A Norwegian family [4], including five HNF-1β mutation carriers in three consecutive generations gave us an opportunity to study the renal disease with regard to long-term clinical follow-up. In order to study the nephropathy in this family in more detail, we obtained kidney biopsies from four of the mutation carriers for light and transmission electron microscopy and morphometric analyses.

METHODS

Subjects

The pedigree of the Norwegian family is shown in Figure 1. Mutation analysis previously demonstrated an in-frame deletion (R137-K161del) in HNF-1β [4].

The study was based on written informed consent, and performed according to the Declaration of Helsinki.

Case I-1. In her twenties, subject I-1 had several epi-

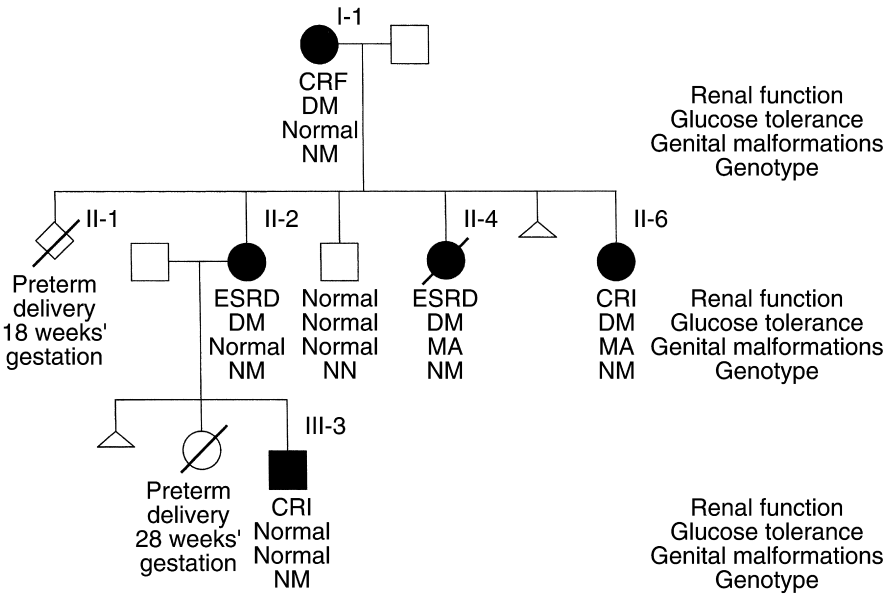

Fig. 1. Pedigree of a Norwegian family with hepatocyte nuclear factor-1β (HNF-1β) (R137-K161del) mutation. Filled symbols indicate affected subjects, while open symbols demonstrate healthy individuals. Abbrevations are: CRF, chronic renal failure; CRI, chronic renal insufficiency; ESRD, end-stage renal disease; DM, diabetes mellitus; N, normal allele; M, mutated allele; MA, Müllerian aplasia.

sodes of pyelonephritis. At age 42 years she was admitted to hospital with proteinuria and reduced kidney function (serum creatinine 153 μmol/L; normal range 65 to 100 μmol/L). Renal ultrasonography revealed a small right kidney with increased echo density, a normal left kidney, and no cysts. Intravenous pyelography (IVP) demonstrated papillary changes consistent with earlier pyelonephritis. Proteinuria was present during every pregnancy, the first at age 25 years. During her fourth pregnancy (age 36 years), gestational diabetes was diagnosed, and impaired glucose tolerance (IGT) sustained after delivery. She developed manifest diabetes 52 years old. Antihypertensive treatment was initiated at age 51 years. Chronic renal failure (CRF) was diagnosed when she was 52 years old with serum creatinine of 228 μmol/L. At age 57 years, serum creatinine was 285 μmol/L and elevated microalbuminuria was present (0.048 g/L; normal range 0 to 0.020 g/L). Renal ultrasonography demonstrated small kidneys with loss of renal parenchyma and small cysts in the right kidney.

Case II-2. Proteinuria was detected at a school health screening when the female patient was 10 years old. IVP demonstrated normal renal anatomy. Reduced filling within the renal pelvices was interpreted as reduced kidney function. Renal ultrasonography at age 13 showed abnormal echo density and no cysts. Renal biopsy demonstrated reduced number and enlarged nephrons with hypertrophy of the proximal tubules, consistent with oligomeganephronia. Shortly after a delivery at the age of 22 years, she developed diabetes, initially treated with insulin, but later with diet. Blood pressure was consistently normal. End-stage renal disease (ESRD) was diagnosed when she was 28 years old, and a kidney transplantation was done.

Case II-4. At age 6 months, the female patient had convulsive seizures. An electroencephalogram (EEG), x-ray film of the skull, and fasting blood glucose were normal. Subsequently, she showed failure to thrive and delayed psychomotor development. Slight metabolic acidosis suggested a renal tubular disorder. IGT was documented at age 16 months. Intermittent proteinuria was observed when she was 4 years old. IVP at age 7 years demonstrated reduced contrast filling within both kidneys. Multicystic left kidney was registered at the age of 7 years during an attempted surgical biopsy. Gynecologic examination and rectal ultrasonography at age 22 years revealed vaginal aplasia, rudimentary uterus, but normal ovaries. Serum creatinine increased progressively with age (Fig. 2), and ESRD was diagnosed when she was 20 years old. Her blood pressure was normal. Renal transplantation was performed at age 21 years. During treatment with glucocorticoids, she developed insulin-requiring diabetes. From 22 years on, she developed a condition resembling multiple sclerosis. The condition progressed into skeletal muscle paralysis, blindness, and motoric aphasia. She died aged 27.

Case II-6. When the female patient was 11 years old, elevated serum creatinine, reduced urine concentration capacity, and nocturnal enuresis were observed. Renal ultrasonography was normal. At age 14 years, she was diagnosed with insulin-requiring diabetes. Computed tomography showed normal renal parenchyma and liver. At 17 years old, a gynecologic examination revealed vaginal aplasia and rudimentary uterus. Serum concentrations of sex hormones and cortisol were normal. Urine microalbumin of 0.084 g/L (normal range 0 to 0.020 g/L) and chronic renal insufficiency (CRI) were observed at the age of 18 years. Blood pressure was normal.

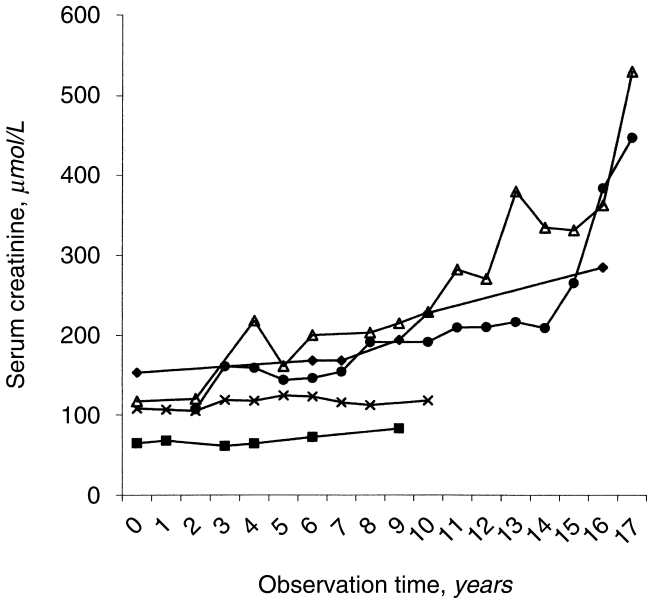

Fig. 2. Serum creatinine during an observation time from 9 to 17 years in five subjects from a Norwegian family with hepatocyte nuclear factor-1β (HNF-1β) mutation. Each value represents the mean of all measurements obtained during 1 year. Symbols: Subject I-1 (◆); Subject II-2 (●); Subject II-4 (△); Subject II-6 (×); Subject III-3 (■).

Case III-3. After a premature delivery, the male patient presented with neonatal hypoglycaemia and failure to thrive. Metabolic acidosis, glucosuria, generalized amino aciduria and slight proteinuria were observed 10 days after delivery. At 3 months old, serum creatinine was in the upper normal range (67 μmol/L; normal range 35 to 80 μmol/L). Renal ultrasonography demonstrated slightly increased echo density of the renal parenchyma without cysts. Two years later, the amino aciduria was nearly normalized. When he was 6 years old, an oral glucose tolerance test was normal. Ultrasonography revealed normal internal genital organs and left kidney, while the right kidney had increased echo density with a subcortical cyst. Urine microalbumin was elevated (0.048 g/L; normal range 0.000 to 0.020 g/L). At age 9 years, a renal ultrasonography revealed four cortical cysts in the right kidney, while an irregular structure with increased echo density was observed in the upper pole of the left kidney. Serum creatinine was 82 μmol/L and creatinine clearence was 61 mL/1.73 m^2. Blood pressure was normal.

Materials

In the mutation carriers, renal biopsies were obtained from four cases in three consecutive generations (cases I-1, II-2, II-6, and III-3). Percutaneous renal biopsies were obtained by ultrasound guidance using a 16-gauge needle. The biopsy specimens were formalin-fixed, paraffin-embedded, and prepared for light microscopy and immunohistochemistry. Material for transmission electron microscopy was fixed in a formaldehyde-glutaraldehyde mixture and postfixed in osmium tetroxide.

Light and transmission electron microscopy. Hematoxylin and eosin (H&E) and periodic-acid Schiff (PAS), or toluidine blue (case III-3)-stained slides were examined by light microscopy. Changes in glomeruli, tubulointerstitial tissue, and vessels in addition to the diameters of the Bowman's space, glomerular tufts, and the tubules were recorded. The thickness of the glomerular basement membrane (GBM) was measured from the electron micrographs.

Morphometric measurements. The morphometric measurements done on the biopsies from our cases were compared with results from three control groups consisting of biopsies obtained from the Norwegian Kidney Registry at Department of Pathology, Haukeland University Hospital. Control group 1 included biopsies from 13 adult subjects with diabetic nephropathy. Control group 2 included 11 adult subjects in whom renal biopsy was done due to glomerulonephritis or benign nephrosclerosis. Renal biopsies from 12 children showing minimal-change glomerulopathy or glomerulonephritis constituted control group 3.

All morphometric measurements were performed by the same investigator (J.V.S.) and controlled by an experienced nephropathologist (L.B.). From the mean value of the perpendicular diameter of Bowman's space and glomerular tuft, the area was calculated. In the mutation carriers, the measurements were performed in the number of glomeruli present in each slide (all slides contained less than 10 glomeruli), while in the control groups, 10 different glomeruli were selected in each specimen. The mean values of the perpendicular diameter of the proximal and distal tubules were obtained. The GBM thickness was measured from the electron micrographs at ×6000 or ×8800 magnification. The GBM width was recorded at 20 different randomly selected sites. Results from six patients of control group 1, five patients in control group 2, and seven patients in control group 3 were selected for these measurements.

Statistical analysis

Statistical analyses were performed between control groups 1 and 2. This was done with Mann-Whitney U test using an SSSP 11.0 package. A P value less than 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Clinical characteristics of the mutation carriers are presented in Table 1. Renal disease was diagnosed at 11 ± 7 years (range 3 to 20 years) prior to diabetes in four cases (I-1, II-2, II-4, and II-6), whereas subject III-3 is still normoglycemic. As shown in Figure 2, renal func-

Table 1. Clinical characteristics of subjects from a Norwegian family with a hepatocyte nuclear factor-1β (HNF-1β) mutation

ID	Gender *F/M*	Present age *years*	Renal biopsy *age in years*	Renal disease diagnosed *age in years*	Serum creatinine *μmol/L*[a]	U-albumin *g/L*[b]	Renal cysts +/−	Diabetes mellitus diagnosed age in *years*	Hypertension +/−
I-1	F	58	57	42	285	0.048	+	52[c]	+
II-2	F	33	13	10	453	0.449	−	22	−
II-4	F	27[f]	NA	1	643	NA	+	21[d]	−
II-6	F	22	21	11	118	0.084	−	14	−
III-3	M	10	9	3 months	82	0.048	+	NGT[e]	−

Abbreviations are: F, female; M, male; NA, not available; NGT, normal glucose tolerance; IGT, impaired glucose tolerance.
[a] Reference values (adult females 65 to 100 μmol/L; children 35 to 80 μmol/L)
[b] Normal range 0.000 to 0.020 g/L
[c] Gestational diabetes at age 35 years, IGT after delivery
[d] IGT at age 1 year, manifest diabetes 21 years old
[e] Intermittent glucosuria, borderline oral glucose tolerance
[f] Age at death

Table 2. Morphometric measures in renal biopsies from four subjects with hepatocyte nuclear factor-1β (HNF-1β) mutation compared with control groups

ID	Glomerular tuft μ^2	Bowman's space μ^2	Proximal tubules *diameter, mm*	Distal tubules *diameter, mm*	GBM *thickness, nm*[c]
I-1	25,873, 31,731 (2)[a]	33,168, 61,136 (2)[a]	115 ± 25 (10)[a]	77 ± 19 (10)[a]	363 ± 100
II-2	83,029 ± 12,946 (3)	111,263 ± 18,687 (3)	120 ± 25 (10)	61 ± 2 (5)	379 ± 96
II-6	40,862 ± 6009 (4)	49,392 ± 8260 (4)	84 ± 17 (10)	60 ± 11 (10)	333 ± 63
III-3	14,447 ± 3210 (4)	15,679 ± 3524 (4)	62 ± 10 (10)	53 ± 13 (5)	341 ± 79
Control group 1 (N = 13)	26,523 ± 9853 (10)	31,552 ± 11,113 (10)	65 ± 15 (10)	45 ± 10 (10)	649 ± 194 (6)[b]
Control group 2 (N = 11)	22,105 ± 6209 (10)	26,596 ± 6867 (10)	61 ± 10 (10)	43 ± 8 (10)	374 ± 74 (5)[b]
Control group 3 (N = 12)	17,825 ± 5800 (10)	20,799 ± 6533 (10)	60 ± 8 (10)	42 ± 7 (10)	348 ± 106 (7)[b]

Abbreviations are: GBM, glomerular basement membrane.
Data are presented as mean ± SD.
[a] The number of structures measured in each case are given within parenthesis
[b] Number of cases included in each control group for measurement of the GBM thickness
[c] Twenty separate measurements of the GBM in each biopsy

tion was monitored for 9 to 17 years. The two youngest patients (II-6 and III-3) had stable or slightly increasing serum creatinine. In two cases (II-2 and II-4), a moderate increase of serum creatinine over several years was followed by a serious progression toward ESRD and kidney transplantation. The eldest family member (I-1) presented CRI much later at the age of 42 years, followed by a moderate increase of the serum creatinine toward CRF 10 years later.

Morphometric measurements

Area of the glomerular tuft and Bowman's space. Cases I-1, II-2, and II-6 showed increased area of the glomerular tuft and Bowman's space compared with patients diagnosed with benign nephrosclerosis and/or glomerulonephritis (control group 2 and 3), as shown in Table 2 and Figure 3 A and B. In control group 1, the diabetic nephropathy group, there was as expected increased glomerular area compared to control group 2 ($P < 0.0001$). The glomerular area in one mutation carrier (II-2) was considerably larger than in group 1, whereas cases I-1 and II-6 had glomerular sizes comparable with diabetic nephropathy. Subject III-3, on the other hand, demonstrated normal-sized glomeruli.

Proximal and distal tubules. Hypertrophy of the proximal and distal tubules was found in mutation carriers I-1, II-2 and II-6, compared with control groups (Fig. 3 C and D). This hypertrophy was not found in case III-3, although the distal tubules were widened in this mutation carrier as well.

Glomerular basement membrane. The thickness of the GBM in the mutation carriers was found to be near normal (Table 2). As expected, control group 1 showed increased GBM width. Case II-2 had slightly increased GBM thickness (379 ± 96 nm) compared with cases I-1 (363 ± 100 nm) and II-6 (341 ± 79 nm). Mutation carriers did not differ from control groups 2 and 3 regarding GBM thickness.

Morphologic examinations

Except for the enlarged nephrons, the renal biopsies from all family members revealed nearly normal morphology (Fig. 4). A few small areas of focal tubulointerstitial scarring with some scattered mononuclear inflammatory cells were found. In patients I-1 and II-6, there was glomerular mesangial positivity for IgM and C1q. Arteriolosclerosis was not shown in any of the renal biopsies from the mutation carriers. No electron-dense deposits or other significant findings were found by transmission electron microscopy.

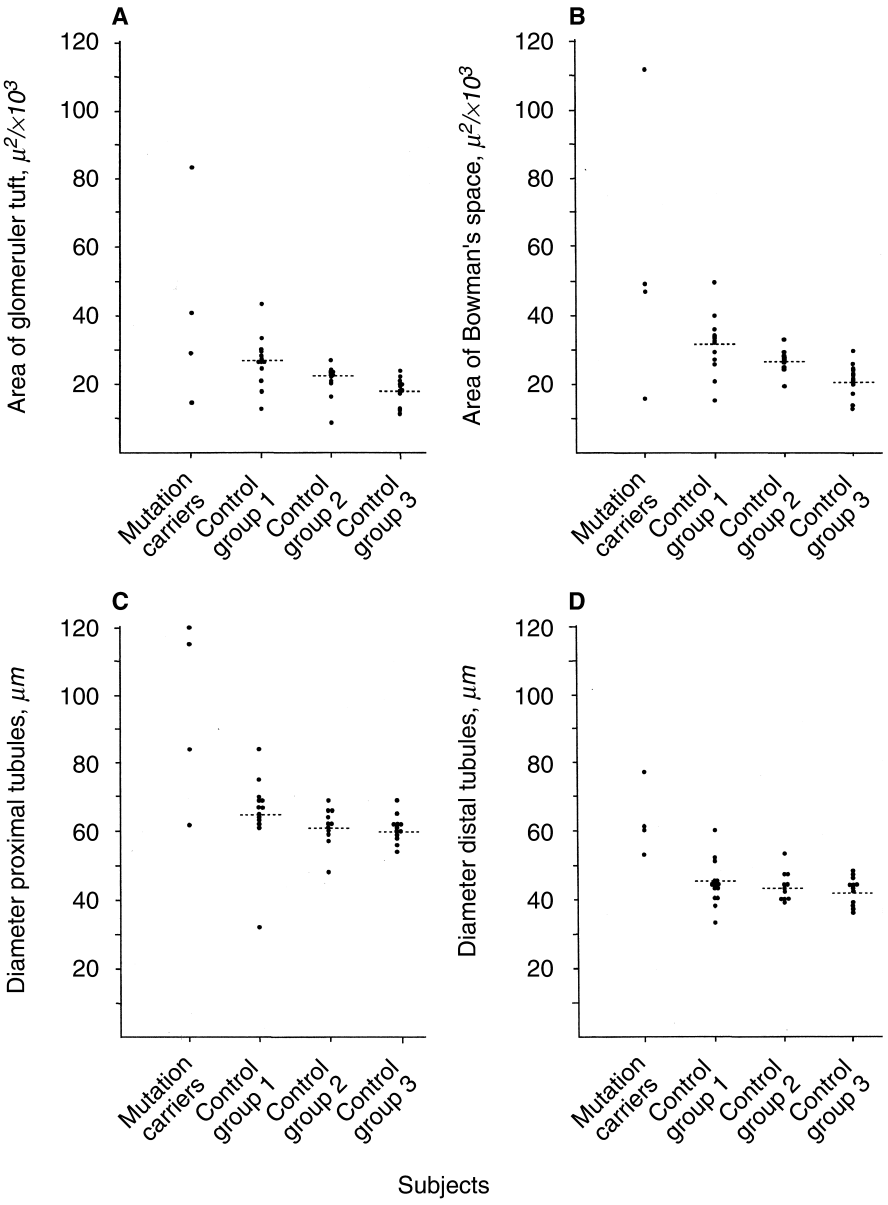

Fig. 3. Morphometric measurements in kidney biopsies from four patients with a hepatocyte nuclear factor-1β (HNF-1β) mutation and three control groups (control group 1, 13 adult subjects with diabetic nephropathy; control group 2, 11 adult subjects with glomerulonephritis or benign nephrosclerosis; and control group 3, 12 children with minimal change glomerulopathy or glomerulonephritis). The area of the glomerular tuft (*A*), Bowman's space (*B*), diameter of the proximal tubules (*C*), and distal tubules (*D*) were measured. Dots indicate results obtained in individual subjects, while transverse lines represent mean values. For the mutation carriers, one dot represents the mean value of 2-5 (A and B), or 5-10 (C and D) measurements, whereas control values are based on 10 measurements for each subject.

DISCUSSION

We have performed morphometric analyses of nephrons in renal biopsies from patients with an HNF-1β mutation, and demonstrated enlargement of glomeruli as well as tubular structures. There was considerable intrafamilial variation among the cases studied. Thus, a 13-year-old girl (case II-2) showed a pattern of oligomeganephronia [12, this report], with a reduced number of markedly enlarged nephrons, whereas the nephrons of a 10-year-old boy (case III-3) appeared as structurally near normal.

A similar phenotypic variation was found with respect to the genital anomalies observed. Two females (cases II-4 and II-6) had Müllerian aplasia, with vaginal aplasia and rudimentary uterus, whereas two other female mutation carriers (cases I-1 and II-2) had had normal child births. The phenotypic expression in this family is further complicated by the fact that the presence of genital anomalies was not necessarily associated with severe renal disease. Nevertheless, we feel justified to conclude that in this family there is a fundamental urogenital developmental defect related to the HNF-1β mutation. Since one of our patients displayed a pattern of oligomeganephronia and this diagnosis was considered possible in two other mutation carriers, one may speculate that the underlying renal defect in our patients relates to a reduced number of nephrons. Unfortunately, due to scarcity of biopsy material, this question could not be addressed in detail.

The long-term clinical follow-up of this family demon-

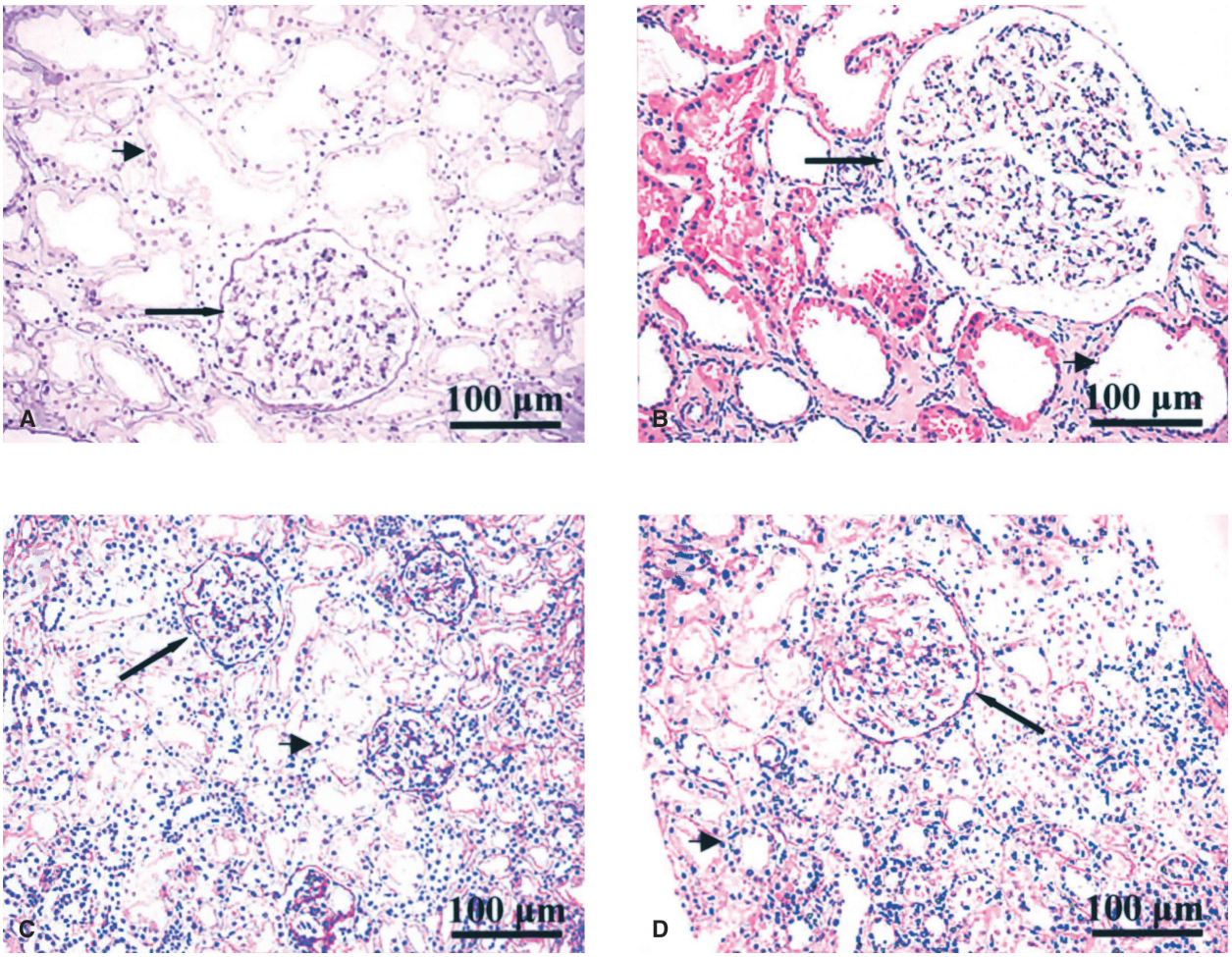

Fig. 4. Representative light microscopy of renal biopsies from case II-6 (panel 1), case II-2 (panel 2), a child from control group 3 with IgA nephropathy (panel 3) and an adult patient with diabetic nephropathy (panel 4). The large arrows point to the glomeruli, and the arrow heads point to the tubules. The black bar is 100 µm. All microphotographs have the same degree of magnification (×40 objective).

strates the early appearance and severity of renal disease, compatible with a congenital disorder. In subject II-4, there was evidence of a glomerular and tubular disorder already in infancy, followed by increasing serum creatinine during childhood and adolescence, and renal transplantation at age 21 years. Case II-2, with oligomegaphronia detected at age 13 years, had a renal transplant 15 years later.

Since diabetes mellitus is present in most cases with HNF-1β mutations, and was observed in four of our patients, we considered the possibility of a diabetic nephropathy. Glomerular enlargement in addition to thickening of the GBM are well-known structural changes in diabetic nephropathy [16–18]. However, the following arguments speak against such a possibility: (*1*) our patients showed microalbuminuria and increasing serum creatinine prior to clinical diabetes; (*2*) renal ultrasonography showed small or normal sized kidneys, contrary to enlarged kidneys in early diabetic nephropathy; (*3*) the GBM thickness was considered near normal in all mutation carriers; (*4*) there was no evidence of arteriolosclerosis in our patients; and (*5*) our patients presented a relatively mild diabetes, with only slightly elevated levels of glycosylated hemoglobin.

Proteinuria may be associated with tubulointerstitial inflammation, renal scarring, and proximal tubular cell proliferation [19–21]. The renal biopsies from our patients showed, in addition to tubular hypertrophy, only small focal areas with scarring and scattered cellular infiltrates. However, the low-to-moderate urinary albumin concentrations observed, probably played no significant role in the renal pathology of the patients. Likewise, hypertension may be excluded as a pathogenic factor, since increased blood pressure was measured in one subject only (case I-1), at the age of 51 years.

Table 3 summarizes published histopathologic studies of renal biopsies in HNF-1β mutation carriers in addition to the data presented here. Renal involvement (cysts,

Table 3. Summery of light microscopic studies of renal biopsies in hepatocyte nuclear factor-1β (HNF-1β) mutation carriers

Mutation	P328L329fsdelCCTCT	E110X	P159fsdelT Same family		Q243fsdelC	P334fsinsC	R137-K161del Same family			
ID	III-1	III-4	II-2	III-1	IV-1	III-1	I-1	II-2	II-6	III-3
Pathologic diagnosis	Abnormal nephrogenesis	GCKD	GCKD	GCKD	Cystic dysplasia	GCKD	Enlarged nephrons	Oligomeganephronia	Enlarged nephrons	Unspecific changes
Age at biopsy	17 weeks of gestation	4 years	10 months	3 years	2 months	4 months	57 years	13 years	21 years	9 years
Reference	[15]	[13]	[13]	[13]	[6]	[14]	[this report]	[4, this report]	[this report]	[this report]

Abbreviations are: GCKD, glomerulocystic kidney disease.

CRI, CRF, ESRD) was present in 47 patients, and absent in four mutation carriers, whereas this was not commented on three cases. Glomerulocystic kidney disease or cystic dysplasia, which is reported in the literature, was not found in our biopsy cases. A cystic kidney was observed in case II-4 during a surgical intervention, where no biopsy was obtained. The hypertrophy of the nephrons observed in our patients has not been reported by other investigators. In a total of 54 cases [1, 2, 4–7, 13–15, 22–25] the kidney disease was diagnosed prior to diabetes in 29 patients, whereas the opposite was true in 11 subjects. In 14 mutation carriers, this question was not addressed. Thirty-seven patients had diabetes mellitus or IGT, whereas normoglycemia was reported in 14 mutation carriers. Totally, six mutation carriers (five female and one male mutation carriers) had malformations of the genital tract.

CONCLUSION

Morphometric studies of kidney biopsies from a family with HNF-1β mutation carriers demonstrated enlarged glomeruli and tubular structures. The present and previously published reports underscore the wide interfamilial and intrafamilial phenotypic variation of the renal disease associated with HNF-1β mutations. The long-term clinical follow-up illustrates the natural history of the renal disease associated with HNF-1β mutation, and together with the histopathologic examinations it strongly suggest that the nephropathy starts prior to and independently of diabetes.

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