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Renal function and blood pressure five years after Puumala virus-induced nephropathy

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Background. Nephropathia epidemica (NE) is a mild form of hemorrhagic fever with renal syndrome caused by Puumala hantavirus. Its long-term prognosis is considered favorable. Some reports suggest, however, that a previous hantavirus infection increases the risk of hypertension.

Methods. We studied 46 previously healthy subjects (26 males and 20 females, mean age of 44 years) who had serologically confirmed NE three to seven years previously, and 38 healthy, seronegative controls (22 males and 16 females, mean age of 44 years). Ambulatory blood pressure (ABP) was monitored. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by ^{51}CrEDTA and ^{131}I-hippurate clearances, respectively. The filtration fraction (FF) was calculated. Quantitative 24-hour urinary protein excretion ($U_{prot}E$) and timed overnight urinary excretion of α_1-microglobulin were measured.

Results. The NE patients had a higher mean ambulatory systolic BP than the controls (123 ± 13 vs. 117 ± 9 mm Hg, $P = 0.008$). GFR and FF were increased in patients compared with controls (GFR, 120 ± 20 vs. 109 ± 14 mL/min/1.73 m^2, $P = 0.006$; FF, 19 ± 3 vs. 18 ± 3%, $P = 0.030$), but ERPF did not differ between the groups. The patients also had higher UPE than the controls (median 0.18 g/day, range 0.12 to 0.38 vs. median 0.14 g/day, range 0.09 to 0.24, $P < 0.001$, respectively). The overnight urinary excretion rate of α1-microglobulin exceeded 7 μg/min in nine patients.

Conclusion. Three to seven years after NE, the patients had higher GFR and FF, more proteinuria, and higher ambulatory systolic BP compared with the healthy controls. NE may thus cause mild renal lesions and alterations in BP in some patients.

Nephropathia epidemica (NE) is a mild type of hemorrhagic fever with renal syndrome (HFRS). It occurs in Finland, northern parts of Scandinavia, and several other areas in Europe [1]. Approximately 1000 serological diagnoses are made in Finland annually, but judging from the high seroprevalence (5%) in the population, most infections are subclinical or undiagnosed [2]. NE is the most common cause of acute nephritis in Finland [3]. The causative agent, Puumala (PUU) virus, is a member of the genus *Hantavirus* in the *Bunyaviridae* family [4]. Its natural host is the bank vole *(Clethrionomys glareolus)* [5].

The HFRS viruses, including PUU, Dobrava, Hantaan, and Seoul [1], cause an acute illness characterized by high fever, headache, back and abdominal pains, nausea, vomiting, visual disturbances, and hemorrhages [6, 7]. There is considerable variability in the clinical severity of NE, ranging from subclinical to occasionally fatal disease [8]. Host-genetic factors obviously have an influence on the clinical course of NE [9].

In many cases, the clinical course follows certain phases: febrile, hypotensive, oliguric, polyuric, and convalescent [10]. Impairment of renal function is commonly seen in hospital-treated patients, characterized by atzotemia, microscopic hematuria, and proteinuria, and transient hemodialysis is needed in a minority [7]. The typical renal histopathologic lesion is acute tubulointerstitial nephritis [11]. Proteinuria is mostly due to a loss of albumin, reflecting glomerular injury [10]. Concomitant urinary loss of low molecular weight proteins such as β2-microglobulin indicates that tubular injury also contributes to the proteinuria [12].

The convalescent phase may last from three weeks to three months [12, 13]. The long-term prognosis of NE is usually considered favorable. However, previous follow-up studies in HFRS patients for up to five years after acute disease have shown a slightly impaired concentration capacity reflecting renal tubular defects in a minority of patients [13–16]. In a Finnish study, endogenous creatinine clearance was decreased in 5 out of 20 and renal concentration capacity was decreased in 8 out of 20 patients one to six years after acute NE [13]. More-

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over, studies by one group in the United States suggest that previous hantavirus infection might be associated with an increased risk of hypertensive renal disease, a phenomenon that may have considerable public health and economic implications [17, 18].

We undertook the present study to investigate whether NE is followed by long-term alterations in renal function and blood pressure (BP).

METHODS

Study population

The study involved 46 subjects who suffered from NE three to seven (mean 5) years previously. The cohort comprised 26 males and 20 females aged from 24 to 62 (mean 44) years. They were hospitalized at the Department of Internal Medicine, Tampere University Hospital, Finland, during the period from October 1990 to September 1995 because of serologically confirmed acute PUU virus infection [19]. Acute impairment of renal function was observed in 85% of the patients. The highest serum creatinine concentrations found during hospital care ranged from 75 to 1645 (median 237) μmol/L. Five patients required transient dialysis therapy.

The study was carried out from September 1996 to April 1999 at the outpatient department in Tampere University Hospital. Detailed past and current medical histories were obtained, and a careful physical examination was made. Since the aim was to establish whether NE induces alterations in renal function and BP, the following exclusion criteria were used: diabetes mellitus, hypertension, and renal disease prior to NE. The following diseases previous to NE were noted in six patients: ankylosing spondylarthritis in two, mild bronchial asthma in two, and coronary heart disease and chronic schizophrenia in one each. One of the patients with asthma also had postoperative hypothyroidism. All of these patients continued to use their medication over the period of study.

A diagnosis of essential hypertension was made, and antihypertensive treatment (bisoprolol and indapamide) commenced at a healthcare center in one female patient one year after NE. She used her medication during the study. Elevated BP values (>140/90 mm Hg) were recorded in three cases from the time of their acute phase of NE, but no medication was adopted. Furthermore, hypertensive values were noted in one patient two years after the infection; here too, no treatment had been undertaken.

We also studied analogously 38 healthy controls who were seronegative for PUU virus. The control group comprised 22 males and 16 females aged from 26 to 64 (mean 44) years. Voluntary controls were collected by open advertisement. The controls had the same exclusion criteria as the patients: a history of diabetes mellitus, hypertension, and renal diseases. Of the controls, one female was using thyroxin substitution for hypothyreosis and was considered euthyreotic. The patient and control groups were comparable to each other in respect of age, gender, and body mass index (BMI), since these variables contribute substantially to BP and parameters reflecting renal function. BMI was calculated by dividing weight (kg) by the square of height (m^2). The socioeconomic status of each patient and control was classified into one of three groups (group A, self-employed persons and upper level employees; group B, lower level employees and manual workers; and group C, others, including students and pensioners).

All subjects gave informed consent before participation, and the study was approved by the Ethics Committee of Tampere University Hospital.

Blood specimens

Blood samples were obtained in the morning after a minimum 12-hour fast. Serum creatinine, urea, sodium, potassium, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and blood glucose were determined by Vitros (Johnson & Johnson, Rochester, NY, USA), and a blood cell count was completed by Technicon H3 (Bayer Diagnostics, Elkhart, IN, USA).

Electrocardiogram

A 12-lead resting electrocardiogram (ECG) was obtained. The sum of the height of the S wave of lead V1 and the R wave of lead V5 was calculated and reported as SV1 + RV5 (mm) as a measurement of left ventricular hypertrophy (LVH).

Determination of renal function

The glomerular filtration rate (GFR) was determined by the plasma clearance of ^{51}CrEDTA, assessed by a single-injection method. Effective renal plasma flow (ERPF) was estimated by clearance of ^{131}I-hippurate. The filtration fraction (FF) was calculated as the quotient of GFR and ERPF. GFR is expressed in both absolute values (GFR_{abs}) and values normalized for body surface area.

Urine specimens

The study subjects were instructed to perform a fractionated 24-hour urine collection at home. The nightly collection period was measured from the time of the last voiding (into the toilet) at bedtime until the last voiding (into a polyethylene plastic receptacle) upon rising. The daytime collection commenced immediately thereafter and lasted until the total 24 hours were completed in the evening. After completion, volumes were measured and timing was recorded for the two collection periods.

Quantitative 24-hour urinary protein excretion ($U_{prot}E$)

was measured by the pyrogallol red molybdate method (Olli C.; Kone Instruments, Helsinki, Finland) and was calculated as a sum of the nightly and daily protein excretions. Timed overnight urinary excretions of α_1-microglobulin, albumin (UAER) and IgG were measured by nephelometry (Behring Nephelometer II Analyzer; Behringwerke AG, Marburg, Germany). Overnight urinary excretions of α1-microglobulin $\geq$7 μg/min, albumin $\geq$11 μg/min, and IgG $\geq$5 μg/min were considered abnormal based on the healthy reference material of our laboratory.

Spot samples of morning urine were collected after a minimum 12-hour fast. Second-morning urine specimens were analyzed for osmolality and were tested with dipsticks for erythrocytes, leukocytes, albumin, nitrite, glucose, pH, and ketones. A microscopic urine examination was made if dipstick tests showed positive results for erythrocytes, leukocytes, protein, or nitrite. Hematuria was defined as a positive dipstick test for erythrocytes and over two erythrocytes per high-power field. Osmolality of urine was measured by the Advanced Cryomatic™ Osmometer (Advanced Instruments Inc., Needham Heights, MA, USA).

Ambulatory blood pressure monitoring

Twenty-four–hour ambulatory BP (ABP) was measured during one 24-hour period by the oscillometric and/or auscultatory method using a noninvasive, fully automatic recorder (Novacor Diasys Integra; Novacor SA, Rueil-Malmaison France). An experienced nurse fitted the device, and BP was verified against a mercury sphygmomanometer upon installation and removal. At the start of each ambulatory BP monitoring (ABPM) registration, three measurements were taken with the Novacor Diasys Integra monitor in the outpatient clinic. The means of these three readings were taken as office BPs. Thereafter, readings were recorded at 15-minute intervals during the daytime and at 30-minute intervals during the night. The subjects were advised to pursue their usual daily routines and to keep a record of their activities. None were on night shift duties, and all slept during the night.

Analysis of the ambulatory blood pressure data

Irregularities in BP readings were rejected automatically or manually after visual inspection, when systolic BP (SBP) was $<$50, diastolic BP (DBP) was $<$30 or $>$150 mm Hg, and heart rate was $<$35 or $>$250 beats per minute. Mean values for SBP and DBP, mean BP (MBP), and heart rate were calculated from each registration during the 24-hour day-and-night period. Circadian variability (%) was calculated as follows: (daytime value $-$ nighttime value) $\times$ 100/daytime value. MBP was calculated as follows: DBP + 1/3(SBP $-$ DBP). The cutoff point for ABP used to define "hypertension" was a 24-hour mean ABP of more than 133/82 mm Hg with reference to a large population study of ABPM [20].

Statistical analysis

To describe the data, means and standard deviations are given for normally distributed variables and medians and ranges for skew-distributed continuous variables. For categorical variables, percentages are used.

Groups were compared using independent sample *t*-tests for normally distributed variables and Mann–Whitney *U* tests for skewed variables. As concentrations of proteins in urine from healthy individuals were frequently below the detection limit of nephelometry, they were dichotomized (protein yes/no), and differences between groups tested using cross-tabulation and χ^2 test or Fisher's exact test. Pearson's correlation coefficients were used to examine relationships between normally distributed continuous variables. In view of their skewed distribution, $U_{prot}E$, UAER, and maximal creatinine concentrations during the acute phase of NE were log transformed before analysis. Multiple linear regression analysis was carried out to identify factors determining proteinuria in the patient group. Analysis of covariance was made to determine whether the difference in proteinuria and GFR_{abs} between the groups could be ascribed to a difference in factors other than the previous NE disease. All testing was two sided, and statistically significant *P* values are given. All tests were performed with the SPSS (version 7.0) statistical software package.

RESULTS

Clinical data and biochemical profile

The essential clinical characteristics and results from some basic laboratory tests of patients and controls appear in Table 1. Age, BMI, gender, and basic laboratory tests did not differ between the groups. Furthermore, the groups were comparable in respect of socioeconomic status: 12 out of 38 (32%) controls and 16 out of 46 (35%) patients belonged to group A, 24 (63%) controls and 25 (54%) patients to group B, and 2 (5%) controls and 5 (11%) patients to group C. All were in good health and had no history or signs of a recent infection. None had hyperglycemia or anemia.

Electrocardiogram

Neither the patients nor the controls had pathological Q-waves or ST-segment depressions in their electrocardiogram (ECG) recordings. The patients yielded slightly higher values for the sum of SV1 and RV5 than the controls, but the difference was not statistically significant (26 $\pm$ 9 vs. 23 $\pm$ 6 mm, $P = 0.109$). SV1 + RV5 (mm) in ECG correlated positively with 24-hour MBP in both groups (patients, $r = 0.42$, $P = 0.006$; and controls, $r = 0.43$, $P = 0.011$).

Table 1. Clinical characteristics and basic laboratory values in nephropathia epidemia (NE) patients and controls

	Patients ($N = 46$)	Controls ($N = 38$)	P value
Age *years*	44 ± 10	44 ± 10	NS
Sex *males/females*	26/20	22/16	NS
Body mass index[a] *kg/m²*	26 (19–48)	25 (21–34)	NS
Laboratory measurements			
Blood hemoglobin *g/L*	142 ± 11	141 ± 11	NS
Blood leukocytes *E9/L*	5.9 ± 1.6	5.4 ± 1.3	NS
Fasting serum total cholesterol *mmol/L*	5.1 ± 0.8	5.3 ± 0.9	NS
Fasting serum[a] triglycerides *mmol/L*	1.2 (0.5–17.5)	1.4 (0.5–3.6)	NS
Fasting blood glucose *mmol/L*	4.6 ± 0.5	4.3 ± 0.4	NS

[a] Values are expressed as mean ± SD for normally distributed variables and as median (range) for skew-distributed variables

Table 2. Renal function and proteinuria in NE patients and controls

	Patients ($N = 46$)	Controls ($N = 38$)	P value
Serum creatinine *μmol/L*	77 ± 10	81 ± 13	NS
Serum urea *mmol/L*	5.1 ± 1.1	4.7 ± 1.2	NS
Urine osmolality after overnight fast *mOsm/kg*	757 ± 173	749 ± 221	NS
GFR *mL/min/1.73 m²*	120 ± 20	109 ± 14	0.006
GFR_{abs} *mL/min*	136 ± 25	122 ± 23	0.015
ERPF[a] *mL/min/1.73 m²*	639 (355–854)	627 (480–907)	NS
Filtration fraction %	19 ± 3	18 ± 3	0.030
Urinary protein excretion[a] *g/day*	0.18 (0.12–0.38)	0.14 (0.09–0.24)	<0.001
Urinary protein excretion daytime[a] *g*	0.12 (0.07–0.31)	0.10 (0.06–0.14)	<0.001
Urinary protein excretion nighttime[a] *g*	0.006 (0.003–0.23)	0.004 (0.001–0.12)	<0.001

[a] Values are expressed as mean ± SD for normally distributed variables and as median (range) for skew-distributed continuous variables
Abbreviations are: GFR, glomerular filtration rate; GFR_{abs}, absolute values for GFR; ERPF, effective renal plasma flow.

Renal function

There were no significant differences between patients and controls in serum creatinine, urea, and urine osmolality (Table 2). All subjects had normal serum creatinine (healthy upper reference limits: 100 μmol/L in women and 115 μmol/L in men) and urea concentrations (healthy reference intervals: 2.6 to 6.4 mmol/L in women and 3.0 to 8.5 mmol/L in men). Urine osmolality levels after overnight fasting were below 600 mOsm/kg in 6 (13%) patients and in 8 (21%) controls (P = NS).

The mean GFR of the patients was increased compared with controls, expressed either as absolute values or values normalized for body surface area (Table 2). Only one 45-year-old patient showed a reduced GFR (59 mL/min/1.73 m^2). She was also found to have hypertension, and antihypertensive medication was commenced in a healthcare center one year after NE. Results of $U_{prot}E$ and ABPM in this case are shown in Table 4, patient 8.

A GFR above 130 mL/min/1.73 m^2 indicating hyperfiltration was seen in 13 out of 44 (30%) patients and in 4 out of 38 (11%) controls (P = 0.034). The calculated FF for the patients was also significantly higher than that in controls. ERPF did not differ between the groups (Table 2).

In the patient group, GFR and GFR_{abs} correlated positively with the log-transformed $U_{prot}E$ (r = 0.31, P = 0.04, and r = 0.43, P = 0.004, respectively) and with the severity of the previous NE, as determined by the highest serum creatinine concentration (log-transformed) during the acute phase of NE (r = 0.32, P = 0.03, and r = 0.33, P = 0.03, respectively). There was also a slight positive correlation between GFR_{abs} and mean ambulatory SBP (r = 0.32, P = 0.04) in the patient group.

Urinalysis

The patients had significantly higher 24-hour daytime and overnight $U_{prot}E$ values than the controls (Table 2). Twelve out of 45 (27%) patients and 2 out of 38 (5%) controls had $U_{prot}E$ over 0.22 g/day (P = 0.009), which was the 95th percentile limit for $U_{prot}E$ in the controls. Overnight excretion of α_1-microglobulin exceeded 7 μg/min (healthy upper reference limit) in 9 out of 43 (21%) patients and in 1 of the 38 (3%) controls (P = 0.012). UAER exceeded 11 μg/min (healthy upper reference limit) in six (14%) patients and in one (3%) control (P = 0.114). IgG was not detected in the urine in either patients or controls.

Hematuria was observed in five (11%) patients and in two (5%) controls (P = NS). None had glucosuria. One patient had asymptomatic urinary tract infection, and she was excluded from further urinalysis.

Table 3. Results of 24-hour ambulatory blood pressure measurements in NE patients and controls

Ambulatory blood pressure (mm Hg)	Patients ($N = 42$)	Controls ($N = 37$)	P value
Means of 24 hour			
SBP	123 ± 13	117 ± 9	0.008
DBP	79 ± 7	76 ± 7	NS
Means daytime			
SBP	128 ± 14	121 ± 9	0.016
DBP	82 ± 8	79 ± 7	NS
Means nighttime			
SBP	105 ± 12	100 ± 9	0.036
DBP	68 ± 7	66 ± 7	NS
Mean blood pressure			
24-hour	94 ± 8	90 ± 7	0.019
daytime	97 ± 9	93 ± 7	0.024
nighttime	80 ± 8	77 ± 7	NS
Mean heart rate *beats/min*			
24-hour	75 ± 11	70 ± 6	0.013
daytime	77 ± 11	73 ± 7	0.026
nighttime	62 ± 9	58 ± 7	0.014

Values are expressed as means ± SD.

Abbreviations are: SBP = systolic blood pressure; DBP, diastolic blood pressure.

The log-transformed $U_{prot}E$ of the patients did not correlate with BP or severity of previous NE, as determined by the highest serum creatinine concentration (log transformed) during the acute phase of NE.

In multiple linear regression analysis with log-transformed $U_{prot}E$ of patients as dependent variable and the highest acute-phase serum creatinine (log-transformed), 24-hour SBP and GFR_{abs} as independent variables, the only significant factor determining proteinuria turned out to be GFR_{abs} (data not shown). Analysis of covariance was made to determine which factors contributed to proteinuria and GFR_{abs} and whether the difference between patients and controls was seen after separately adjusting for these covariates. GFR_{abs} had a significant influence on proteinuria ($P = 0.001$), but the difference in proteinuria between the groups remained ($P < 0.001$) after controlling for GFR_{abs}. The difference in proteinuria between the groups was also seen after adjustment for 24-hour SBP ($P < 0.001$). It also emerged that 24-hour SBP had a significant effect on GFR_{abs} ($P = 0.012$). However, when the difference in GFR_{abs} between the groups was adjusted for the effect of 24-hour SBP, the difference between the groups remained ($P = 0.048$).

Blood pressure

Forty-two patients and 37 controls underwent 24-hour ABPM. Monitoring failed for technical reasons in two patients and one control. Two patients refused to take part in this section of the study. The values of the BP parameters obtained by ABPM are shown in Table 3. In both groups, the ABP in the day period was higher than that recorded during the night, reflecting circadian variability. The patients had higher mean ambulatory SBP and DBP than the controls during the 24-hour, day-and-night periods, although the difference was significant only for SBP (Table 3). The patients also had significantly higher MBP than the controls during the 24-hour and day periods and higher heart rate during the whole day. The office BP and the circadian variability for SBP, DBP, and heart rate did not differ significantly between the groups (data not shown).

Seven out of 42 (17%) patients and 2 out of 37 (3%) controls had "hypertension" (24-hour mean ABP >133/82 mm Hg) in ABPM ($P = 0.061$). The results of office BP measurements, ABPM, GFR, $U_{prot}E$, and maximal serum creatinine concentrations found during acute PUU virus infection in these patients are shown in Table 4 (patients 1 through 7). Elevated BP values (>140/90 mm Hg) had been measured in two patients (patients 1 and 3, Table 4) ever since and in one patient (patient 2) two years after the acute phase of NE at a healthcare center, but no medication had been used. Three of these seven patients (patients 2, 3, and 5) also showed slightly increased $U_{prot}E$ and GFR values. In addition to these seven, a diagnosis of essential hypertension had been made and antihypertensive treatment commenced in one female patient one year after NE. She was normotensive in ABPM (patient 8; Table 4). Furthermore, ABPM failed for technical reasons in one female patient (patient 9); she had already been noted to be hypertensive at the time of the NE episode, but had used no medication. Five out of these nine cases suffered from severe renal failure during the acute phase of NE (the highest serum creatinine concentrations ranging from 515 to 1281 μmol/L).

DISCUSSION

Our results show that three to seven years after acute PUU hantavirus-induced NE, patients had a higher GFR and FF, more proteinuria, and higher ambulatory SBP and heart rate compared with seronegative controls. Furthermore, 9 out of 46 patients showed either elevated ambulatory (24-hour mean ABP >133/82 mm Hg) or office BP values after NE. Such findings suggest that NE might have chronic consequences for at least some subjects.

In the present study, all patients were in a good general state of health. In mean values, our patients had increased GFR compared with controls (Table 2). GFR was decreased in only one patient, who was also recorded to have hypertension after NE. Previously, glomerular function has been reported to be either normal or slightly decreased in some patients subsequent to NE [12–15]. In a Swedish study, GFR measured by ^{51}CrEDTA clearance was <85 mL/min in 3 out of 74 patients five months after acute NE [12]. A previous Finnish follow-up study of 20 NE patients over a period of one to six years after acute

Table 4. Sex and age distribution, and results of glomerular filtration, urinary protein excretion and blood pressure measurements of nine patients who showed either elevated ABP values or history of development of hypertension after NE

Patient	Sex and age	GFR *mL/min/1.73 m²*	$U_{prot}E$ *g/day*	Office BP	Means 24-hour	Means daytime	Means nighttime	$S\text{-}Cr_{max}$ *μmol/L*
				mm Hg				
No. 1	M 51	107	0.18	128/92	137/94	143/98	111/77	1281
No. 2	M 42	138	0.38	150/94	135/90	141/94	107/72	915
No. 3	M 49	140	0.29	144/108	142/94	146/97	123/81	515
No. 4	M 54	119	0.20	150/83	136/82	143/86	113/72	918
No. 5	M 44	145	0.22	146/103	137/85	143/89	114/69	1241
No. 6	M 61	103	0.16	168/99	152/97	158/101	126/81	102
No. 7	M 61	121	0.18	153/97	139/88	143/90	124/79	134
No. 8[a]	F 45	59	0.18	119/89	114/76	119/79	96/65	93
No. 9	F 53	104	0.20	140/90	x	x	x	1156

The maximal serum creatinine concentrations during acute phase of NE are also shown.

Abbreviations are: GFR, glomerular filtration rate; $U_{prot}E$, urinary protein excretion, $S\text{-}Crea_{max}$, maximal serum creatinine measured during acute phase of NE; x, data not available.

[a] Used antihypertensive medication during the study

disease showed that endogenous creatinine clearance was decreased (<100 mL/min/1.73 m^2) in 5 out of 20 patients [13]. In that study, the individual patient data also revealed five patients with creatinine clearance above 130 mL/min/1.73 m^2, indicating hyperfiltration [13]. This result is in accord with our findings in some patients of hyperfiltration subsequent to NE.

In theory, GFR values obtained by the plasma clearance of ^{51}CrEDTA could be falsely high by reason of precision errors in the single-injection method, for example, an inaccurate technique for intravenous injection of ^{51}CrEDTA and errors in the timing of blood samples. However, such systematic errors cannot explain the difference between the study groups. GFR can also be falsely high in edematous patients. None of our study subjects had swellings. Furthermore, glomerular hyperfiltration is a frequent early finding in diabetes mellitus [21, 22]. None of our patients had hyperglycemia or glucosuria.

In the present study, the increase in GFR in the patient group was not associated with a proportional increase in renal plasma flow, and thus, the calculated FF was significantly higher in the patients compared with the controls. This suggests an altered balance between the tone of the afferent and efferent glomerular arterioles, which might lead to increased intraglomerular pressure as the mechanism of hyperfiltration.

Hyperfiltration could also result from abnormal transmission of systemic hypertension to the glomerulus through a disturbance in intraglomerular autoregulation. Recently, Schmieder et al found that glomerular hyperfiltration is evident in early essential hypertension during stress-induced sympathetic activation [23]. They suggest that angiotensin II is the pathogenetic link between sympathetic activation and glomerular hyperfiltration. In the present study, analysis of covariance showed that BP indeed had an effect on GFR. Nonetheless, the difference in GFR between the study groups remained after an adjustment for BP. In the future, it will be interesting to see whether the hyperfiltration found in some of our patients continues or whether there is a tendency toward hypofiltration.

Our patients evinced higher UPE during the entire day than the controls (Table 2). On the other hand, the amount of proteinuria in the patients was slight. It is noteworthy, however, that the patients more frequently showed increased urinary excretions of α1-microglobulin than the controls, probably in consequence of a tubular alteration impeding the normal reabsorption of filtered protein. Our findings of mild tubular defects are in accordance with the results of two previous Finnish follow-up studies [13, 15]. In the previously mentioned study of 20 patients made one to six years after acute NE, the renal concentration capacity was shown to be slightly decreased in 8 out of 20 patients [13]. In the later study of nine patients carried out four to five years after acute disease, glomerular function was found to be normal, but there were slightly abnormal values in tubular function tests (acidification and concentration capacity) in five patients [15]. Mild nonspecific changes were seen in renal biopsies, possibly connected with the tubular dysfunction [15]. In a Greek study, 12 patients were examined one to five years after acute hantavirus infection and three with normal creatinine clearance and BP had renal tubular acidosis (RTA); two (one of whom also had incomplete RTA) had reduced urine concentrating ability [14].

Among other mechanisms possibly explaining the difference in proteinuria between the groups in this study are renal hemodynamic changes caused by direct transmission of increased systemic pressure to the glomeruli and hyperfiltration. Both multiple linear regression analysis and analysis of covariance showed that GFR had a significant influence on proteinuria. However, the differ-

ence in proteinuria between the groups remained after controlling for GFR, which suggests that there are also other determining factors, for example, alteration in tubular function in consequence of NE.

The patients as a group had higher ambulatory SBP and MBP than the controls (Table 3). Nine out of 46 patients yielded either elevated ambulatory or office BP values after NE (Table 4). However, a majority of the patients were normotensive in ABPM, suggesting that hypertension is not a frequent sequel to NE. There have been occasional reports of an association between previous hantavirus infection and subsequent hypertension [13, 15–17, 24]. One out of nine NE patients had hypertension in the Finnish follow-up study performed four to five years after acute disease [15]. A study made after the Korean War indicated that 2 out of 13 patients with prior HFRS had hypertensive vascular disease [16]. Moreover, results of a large seroepidemiological survey from Baltimore (MD, USA) suggest an association between a previous infection with a rat-borne Seoul-like hantavirus and an increased risk of hypertensive renal disease [18]. In contrast, a study in Sweden brought out no differences in office BP measurements between 110 PUU virus antibody-positive and 682 antibody-negative individuals [25]. Hypertension did, however, correlate significantly with presence of PUU antibodies in 60-year-old individuals, while no correlation or trends were seen in other age groups [25].

Our patients also had a higher ambulatory heart rate than the controls. We assume that this reflects an increased sympathetic activity among the patients. There are varying opinions as to the hemodynamics in the initial phase of essential hypertension. Nonetheless, irrespective of whether the early phase of essential hypertension arises primarily in consequence of increased cardiac output or increased total peripheral resistance, an increased sympathetic activity is usually held responsible for either hemodynamic disturbance [26].

Nephropathia epidemica is clinically characterized by acute renal failure, sometimes so severe that transient hemodialysis therapy is needed. It would be logical to assume that residuals after NE are associated with its severity. In the present study, GFR in the patients correlated slightly with the severity of renal failure during the previous NE. Furthermore, five out of the nine patients who showed elevated ambulatory or office BP values had evinced substantial renal failure during the acute PUU virus infection. In the U.S. survey, almost all (14 out of 15) individuals seropositive for hantaviruses were clinically hypertensive, although only one of them had had a clinical history of an HFRS illness [17]. It is thus possible that a subclinical hantavirus infection may also have chronic consequences.

We conclude that the prognosis of NE caused by Puumala hantavirus is favorable. Nevertheless, NE may cause mild tubular lesions and hypertension in some patients. Further follow-up is necessary to establish the final outcome.

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REFERENCES

1. Mustonen J, Vapalahti O, Henttonen H, Pasternack A, Vaheri A: Epidemiology of hantavirus infections in Europe. *Nephrol Dial Transplant* 13:2729–2731, 1998
2. Brummer-Korvenkontio M, Vapalahti O, Henttonen H, Koskela P, Kuusisto P, Vaheri A: Epidemiological study of nephropathia epidemica in Finland 1989-1996. *Scand J Infect Dis* 31:427–435, 1999
3. Saha H, Mustonen J, Helin H, Pasternack A: Limited value of the fractional excretion of sodium test in the diagnosis of acute renal failure. *Nephrol Dial Transplant* 2:79–82, 1987
4. Lee HW, van der Groen G: Hemorrhagic fever with renal syndrome. *Prog Med Virol* 36:62–102, 1989
5. Brummer-Korvenkontio M, Vaheri A, Hovi T, von Bonsdorff CH, Vuorimies J, Manni T, Penttinen K, Oker-Blom N, Lähdevirta J: Nephropathia epidemica: Detection of antigen in bank voles and serologic diagnosis of human infection. *J Infect Dis* 141:131–134, 1980
6. Settergren B, Juto P, Trollfors B, Wadell G, Norrby SR: Clinical characteristics of nephropathia epidemica in Sweden: Prospective study of 74 cases. *Rev Infect Dis* 11:921–927, 1989
7. Mustonen J, Brummer-Korvenkontio M, Hedman K, Pasternack A, Pietilä K, Vaheri A: Nephropathia epidemica in Finland: A retrospective study of 126 cases. *Scand J Infect Dis* 26:7–13, 1994
8. Valtonen M, Kauppila M, Kotilainen P, Lähdevirta J, Svartbäck CM, Kosunen O, Nurminen J, Sarkkinen H, Brummer-Korvenkontio M: Four fatal cases of nephropathia epidemica. *Scand J Infect Dis* 27:515–517, 1995
9. Mustonen J, Partanen J, Kanerva M, Pietilä K, Vapalahti O, Pasternack A, Vaheri A: Genetic susceptibility to severe course of nephropathia epidemica caused by Puumala hantavirus. *Kidney Int* 49:217–221, 1996
10. Kanerva M, Mustonen J, Vaheri A: Pathogenesis of Puumala and other hantavirus infections. *Rev Med Virol* 8:67–86, 1998
11. Mustonen J, Helin H, Pietilä K, Brummer-Korvenkontio M, Hedman K, Vaheri A, Pasternack A: Renal biopsy findings and clinicopathologic correlations in nephropathia epidemica. *Clin Nephrol* 41:121–126, 1994
12. Settergren B, Trollfors B, Fasth A, Hultberg B, Norrby SR: Glomerular filtration rate and tubular involvement during acute disease and convalescence in patients with nephropathia epidemica. *J Infect Dis* 161:716–720, 1990
13. Lähdevirta J: Nephropathia epidemica in Finland: A clinical, histological and epidemiological study. *Ann Clin Res* 3(Suppl 8):S1–S154, 1971
14. Elisaf M, Korakis H, Siamopoulos KC: Chronic renal dysfunction in hemorrhagic fever with renal syndrome patients. *Ren Fail* 15:623–627, 1993
15. Lähdevirta J, Collan Y, Jokinen EJ, Hiltunen R: Renal sequelae to nephropathia epidemica. *Acta Path Microbiol Scand Sect A* 86:265–271, 1978
16. Rubini MME, Jablon S, McDowell ME: Renal residuals of acute epidemic hemorrhagic fever. *Arch Intern Med* 106:378–387, 1960

17. Glass GE, Childs JE, Watson AJ, Leduc JW: Association of chronic renal disease, hypertension, and infection with a rat-borne hantavirus. *Arch Virol* (Suppl 1):S69–S80, 1990
18. Glass GE, Watson AJ, Leduc JW, Kelen GD, Quinn TC, Childs JE: Infection with a rat borne hantavirus in US residents is consistently associated with hypertensive renal disease. *J Infect Dis* 167:614–620, 1993
19. Hedman K, Vaheri A, Brummer-Korvenkontio M: Rapid diagnosis of hantavirus disease with an IgG-avidity assay. *Lancet* 338: 1353–1356, 1991
20. Staessen JA, O'Brien ET, Amery AK, Atkins N, Baumgart P, De Cort P, Degaute JP, Dolenc P, De Gaudemaris R, Enström I, et al: Ambulatory blood pressure in normotensive and hypertensive subjects: Results from an international database. *J Hypertens* 12(Suppl 7):S1–S12, 1994
21. Mogensen CE: Microalbuminuria as a predictor of clinical diabetic nephropathy. *Kidney Int* 31:673–689, 1987
22. Wirta OR, Pasternack AI: Glomerular filtration rate and kidney size in type 2 (non-insulin-dependent) diabetes mellitus. *Clin Nephrol* 44:1–7, 1995
23. Schmieder RE, Veelken R, Schobel H, Dominiak P, Mann JF, Luft FC: Glomerular hyperfiltration during sympathetic nervous system activation in early essential hypertension. *J Am Soc Nephrol* 8:893–900, 1997
24. Kleinknecht D, Rollin PE: Hypertension after hemorrhagic fever with renal syndrome. *Nephron* 61:121, 1992
25. Niklasson B, Hellsten G, Leduc J: Hemorrhagic fever with renal syndrome: A study of sequelae following nephropathia epidemica. *Arch Virol* 137:241–247, 1994
26. Lund-Johansen P: Newer thinking on the hemodynamics of hypertension. *Curr Opin Cardiol* 9:505–511, 1994