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Ten-year prognosis of Puumala hantavirus-induced acute interstitial nephritis

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Nephropathia epidemica (NE) is a hemorrhagic fever with renal syndrome caused by Puumala hantavirus. Its long-term prognosis is considered favorable. There are, however, some reports about subsequent hypertension, glomerular hyperfiltration, and proteinuria after previous hantavirus infection. Therefore, we studied 36 patients 5 and 10 years after acute NE, with 29 seronegative controls. Office blood pressure, ambulatory 24-h blood pressure (ABP), glomerular filtration rate (GFR), and proteinuria were examined. Hypertensive subjects were defined as those patients having increased ambulatory or office blood pressure, or receiving antihypertensive therapy. Office blood pressure was used to define hypertension only if ABP was not determined. At 5 years, the prevalence of hypertension was higher among NE patients than in controls (50 vs 21%, $P=0.020$). At 10 years, the difference between the groups was no more significant (39 vs 17%, $P=0.098$). Five years after NE, patients showed higher GFR (121 ± 19 vs 109 ± 16 ml/min/1.73 m^2, $P=0.012$) and urinary protein excretion (0.19 g/day, range 0.12–0.38 vs 0.14 g/day, range 0.09–0.24, $P=<0.001$) than controls. At 10 years, there were no more differences in GFR or protein excretion between the groups (GFR: 113 ± 20 vs 108 ± 17 ml/min/1.73 m^2, $P=0.370$; proteinuria: 0.14 g/day, range 0.07–0.24 vs 0.13 g/day, range 0.06–0.31, $P=0.610$). In conclusion, the 10-year prognosis of NE is favorable, as glomerular hyperfiltration and slight proteinuria detected at 5 years disappeared during the longer follow-up. However, the possibility exists that NE may predispose some patients to the development of hypertension.

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Nephropathia epidemica (NE) is a mild type of hemorrhagic fever with renal syndrome caused by Puumala virus. The virus is a member of the hantavirus genus in the Bunyaviridae family carried by bank voles (*Clethrionomys glareolus*).[1] NE is common in Northern Europe, European Russia, and in parts of Central-Western Europe.[1] Approximately 1000 serological diagnoses of Puumala virus infection are made in Finland annually.[2] However, the seroprevalence in the Finnish population is 5%, implying that most infections are subclinical or remain undiagnosed.

NE is the most common cause of acute nephritis in Finland.[3] The clinical picture of the disease varies in severity, and the usual symptoms are high fever, headache, and back and abdominal pain.[4–6] Renal involvement causes proteinuria, hematuria, and oliguria followed by polyuria.[4–6] A minority of patients need transient dialysis treatment.[6] The most characteristic histopathological lesion in renal biopsy is acute tubulointerstitial nephritis.[7] Glomerular alterations are mild despite often heavy proteinuria. Complete recovery is the usual outcome.[4–6]

The long-term prognosis of hemorrhagic fever with renal syndrome has been considered favorable.[4,5,8] However, we previously found that 5 years after acute NE, the patients had higher systolic blood pressure, glomerular filtration rate (GFR), and more proteinuria than healthy controls.[9] A study by one group in the United States suggests that previous hantavirus infection might be associated with an increased risk of hypertensive renal disease.[10]

The aim of the present study was to investigate the 10-year prognosis of NE. We continued our previous study on the 5-year prognosis of acute NE[9] by inviting the same patients and controls to a follow-up visit. We were interested in putative differences in blood pressure and renal function between the patients and controls, and changes in those variables during the follow-up.

RESULTS

Clinical and laboratory data

The clinical and laboratory variables 5 and 10 years after acute NE are shown in Table 1. There was no difference in

Table 1 | Clinical and laboratory findings of patients and controls 5 and 10 years after acute NE

	5 years			10 years		
	Patients (*N*=36)	Controls (*N*=29)	*P*	Patients (*N*=36)	Controls (*N*=29)	*P*-value
Age (years)	45±10	46±10	0.498	50±10	51±10	0.442
Gender (males/females) (*n*)	20/16	14/15	0.622	—	—	—
BMI (kg/m^2)	27 (19–48)	26 (21–34)	0.215	29 (22–44)	26 (21–33)	0.003
Blood hemoglobin (g/l)	142±11	139±11	0.397	142±13	140±12	0.581
Blood leukocytes (10^9/l)	5.9±1.6	5.5±1.5	0.295	6.1±1.9	6.0±1.8	0.775
Serum creatinine[a] (μmol/l)	77±11	81±14	0.179	68±11	72±14	0.252
Serum urea (mmol/l)	5.1±1.1	4.8±1.2	0.342	5.1±1.2	5.0±1.1	0.713
Serum total cholesterol (mmol/l)	5.2 (3.8–7.1)	5.3 (4.0–7.8)	0.445	5.6 (4.3–8.8)	5.3 (4.0–7.9)	0.213
Serum triglycerides (mmol/l)	1.3 (0.5–3.7)	1.5 (0.5–3.6)	0.347	1.4 (0.5–5.1)	1.2 (0.5–2.4)	0.176
Fasting blood glucose (mmol/l)	4.5±0.5	4.5±0.4	0.838	5.1±0.6	4.6±0.4	0.002
Blood hemoglobin A1c (%)	ND	ND	—	5.4 (4.9–7.1)	5.4 (4.9–6.0)	0.764
Urine osmolality (mOsm/kg)	758±179	730±227	0.585	721±242	637±237	0.166

BMI=body mass index; ND=no data; NE=nephropathia epidemica.
Mean±s.d. are given for normally distributed variables and median (range) for skew-distributed variables.
[a]Different determination method of serum creatinine at 5 and 10 years (see Materials and Methods).

body mass index (BMI) between the patients and controls at 5 years. However, at 10 years, the patients had higher BMI than controls, as BMI had increased 1.8 units in them. Fasting blood glucose was also slightly higher in patients than controls at 10 years, but there was no difference in hemoglobin A1c values. Diabetes controlled by diet had been diagnosed in two patients during the time from 5 to 10 years after acute NE. At 10 years, we found one patient having undiagnosed diabetes (blood hemoglobin A1c 7.1%). Alcohol intake, smoking, or exercise habits did not differ between the patients and controls (data not shown).

Neither patients nor controls displayed any pathological Q-waves or ST-T-wave alterations in electrocardiogram recordings, 5 and 10 years after NE. The sum of SV1 and RV5 did not differ between patients and controls at 5 or 10 years (25 and 23 mm, respectively, at 5 years, $P=0.418$; 24 and 23 mm, respectively, at 10 years, $P=0.433$).

Blood pressure

None of the patients or controls received antihypertensive therapy at 5 years. At 10 years, 7/36 (19%) patients and 2/29 (7%) controls were treated with antihypertensive drugs ($P=0.172$, Fisher's exact test). The patients had started therapy 5–11 years after NE. The antihypertensive medications were angiotensin-converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, calcium channel blockers, and diuretics. All these subjects continued their medication during the examinations at 10 years. It is of note that the ambulatory 24-h blood pressure (ABP) monitoring results did not change if the subjects using antihypertensive therapy were excluded from the statistical analyses.

At 5 years, 2/36 patients did not undergo ABP monitoring, but their office blood pressure was normal. At 10 years, two out of five patients, who did not undergo ABP monitoring, had elevated office blood pressure (166/100 and 158/94 mm Hg). One control with no ABP monitoring at 10 years showed office blood pressure of 140/90 mm Hg.

The results of ABP monitoring, 5 and 10 years after acute NE, are shown in Table 2. The patients had higher systolic (Figure 1a) and diastolic blood pressure than controls at 5 years, but there were no significant differences in ABP at 10 years. The blood pressure of patients was stable at 5 and 10 years (systolic blood pressure 123±13 vs 124±13 mm Hg, $P=0.881$; diastolic blood pressure 79±7 vs 80±8 mm Hg, $P=0.921$, paired-samples *t*-test). However, systolic blood pressure of controls increased during the follow-up from 5 to 10 years (116±9 vs 120±11 mm Hg, $P=0.006$). Diastolic blood pressure of controls did not change (75±7 vs 77±8 mm Hg, $P=0.208$).

In 24-h ABP monitoring, 17/34 (50%) patients and 6/29 (21%) controls had hypertension (mean ABP $\geqslant$133/82 mm Hg[11]) at 5 years ($P=0.020$, Fisher's exact test). At 10 years, ABP monitoring showed hypertension in 6/31 (19%) patients and 2/28 (7%) controls ($P=0.259$).

According to the applied definition of the prevalence of hypertension, there were 17/34 (50%) patients and 6/29 (21%) controls having hypertension at 5 years ($P=0.020$, Fisher's exact test). At 10 years, 14/36 (39%) patients and 5/29 (17%) controls had hypertension ($P=0.098$).

In the whole material, the BMI of hypertensive subjects was higher than that of normotensive subjects at 10 years (30 vs 27, $P=0.019$, independent samples *t*-test). BMI had a weak direct correlation with both systolic and diastolic mean blood pressure in ABP ($r=0.41$, $P=0.001$ and $r=0.28$, $P=0.034$, respectively, Pearson's correlation), but no correlation with blood glucose ($r=0.20$, $P=0.120$).

Renal function and proteinuria

Table 2 and Figure 1b show that 5 years after NE the patients had higher GFR than controls, but during the follow-up from 5 to 10 years, GFR of patients decreased to the same normal level as in controls. The decrease in GFR of patients from 5 to 10 years was significant (121±19 vs 113±20 ml/min/1.73 m^2, $P=0.023$, paired-samples *t*-test). Effective renal plasma flow and filtration fraction did not change in patients or in controls.

As shown in Table 2 and Figure 1c, the NE patients had slightly higher urinary protein excretion than controls at 5

Table 2 | Comparisons of ambulatory blood pressure, renal function, and proteinuria in patients and controls 5 and 10 years after acute NE

	5 years			10 years		
	Patients (*N*=34–36)	Controls (*N*=28–29)	*P*-value	Patients (*N*=31–36)	Controls (*N*=28–29)	*P*-value
Means of 24-h (mm Hg)						
SBP	123±13	116±9	0.010	124±13	120±11	0.208
DBP	79±7	75±7	0.026	80±8	77±8	0.134
Means daytime (mm Hg)						
SBP	127±13	120±9	0.024	128±13	124±11	0.222
DBP	81±8	78±7	0.066	82±8	79±8	0.132
Means night time (mm Hg)						
SBP	106±12	100±9	0.016	108±16	105±13	0.435
DBP	68±7	65±7	0.108	69±10	68±9	0.601
GFR (ml/min/1.73 m^2)	121±19	109±16	0.012	113±20	108±17	0.370
ERPF (ml/min/1.73 m^2)	627±105	615±112	0.652	606±115	592±109	0.623
FF (%)	20±3	18±3	0.071	19±4	19±3	0.670
UPE (g/day)	0.19 (0.12–0.38)	0.14 (0.09–0.24)	<0.001	0.14 (0.07–0.24)	0.13 (0.06–0.31)	0.610

DBP=diastolic blood pressure; ERPF=effective renal plasma flow; FF=filtration fraction; GFR=glomerular filtration rate; NE=nephropathia epidemic; SBP=systolic blood pressure; UPE=urinary protein excretion.
Mean±s.d. are given for normally distributed variables and median (range) for skew-distributed variables.

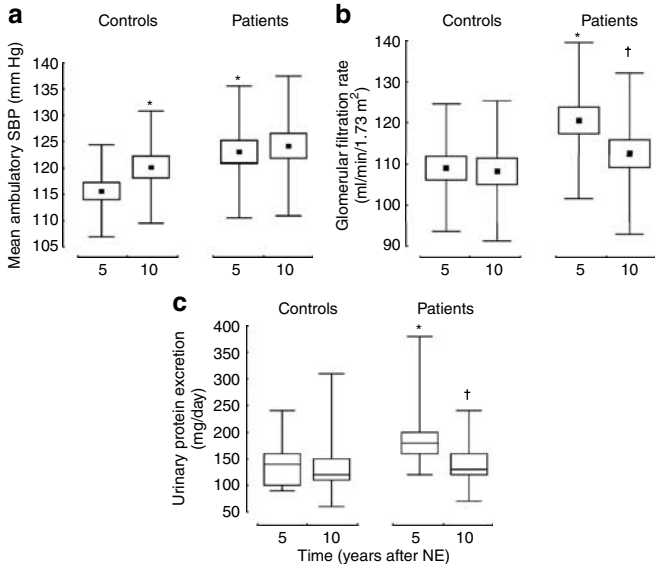

Figure 1 | (a) The 24-h systolic blood pressure, (b) glomerular filtration rate, and (c) urinary protein excretion in controls and patients examined 5 and 10 years after acute NE. The results with normal distribution (**a** and **b**) are depicted as means (■), s.e. of the mean (box), and s.d. (whiskers); results with skewed distribution (**c**) are depicted as medians (line inside box), 25th and 75th percentile (box), and range (whiskers); *$P<0.05$ vs controls at 5 years, †$P<0.05$ vs patients at 5 years.

years. Ten years after acute disease, there was no more difference between the groups, as the slight proteinuria of patients detected at 5 years disappeared during the longer follow-up (0.19 (0.12–0.38) vs 0.14 (0.07–0.24) g/day, $P=<0.001$, Wilcoxon's test). Furthermore, at 5 years the prevalence of elevated urinary α1-microglobulin excretion was also higher in patients than in controls (7/34 vs 1/29, $P=0.060$, Fisher's exact test), whereas at 10 years there was no difference between the groups (4/36 vs 2/29, $P=0.684$). The quantities of overnight urinary excretions of immunoglobulin G or albumin did not differ between the groups at 5 or 10 years (data not shown).

DISCUSSION

This is the first report confirming the present clinical view that the long-term prognosis of Puumala hantavirus-induced acute tubulointerstitial nephritis is favorable. The increased GFR and urinary protein excretion, detected at 5 years, were no more present at 10 years after acute NE. Nevertheless, NE may predispose some patients to the elevation of blood pressure several years after the acute disease. Although the present study was carried out with a relatively small number of subjects, this report is still the largest prospective clinical follow-up trial about the long-term effects of acute NE on blood pressure. All subjects from the original[9] cohort were not available for examinations at 10 years, as 10 patients and nine controls were lost to follow-up. However, if the results at 5 years on GFR, ABP, and proteinuria were calculated excluding the patients lost to follow-up, the outcome was identical whether these individuals were included or excluded. Thus, the remaining patients can be considered to have well represented the original study cohort.

In a combined analysis that defined hypertensive subjects as those having antihypertensive therapy, high blood pressure in ABP monitoring, or high office blood pressure, there were more hypertensive subjects in the patients than in the seronegative controls 5 years after acute NE. At 10 years, the difference between the groups was no more significant. Correspondingly, in the ABP monitoring, systolic blood pressure was higher in patients than in controls at 5 years, but there were no differences between the groups at 10 years. The

systolic blood pressure of controls had increased during the study period, probably as a reflection of aging of the study subjects. In contrast, the blood pressure of patients had remained unchanged from 5 to 10 years. Because of ethical reasons, all subjects receiving antihypertensive therapy continued to use their medication during the examinations at 10 years after NE. As there were more medicated patients than controls at 10 years after NE, this may have influenced the results of the blood pressure measurements.

There have been some reports of a possible association between previous hantavirus infection and subsequent hypertension.[4,10,12–14] Lähdevirta *et al.*[12] from Finland have reported that one out of nine patients presented with hypertension 4–5 years after acute NE. In a study from the Korean War, two out of 13 patients seemed to have hypertensive vascular disease after hemorrhagic fever with renal syndrome.[13] According to a seroepidemiological study from Baltimore, infection with rat-borne Seoul-like hantavirus showed a consistent association with hypertensive renal disease.[10] Furthermore, a study from Sweden reported a significant association between Puumala virus antibody positivity and hypertension in patients over 60 years of age, although such an association was not found in younger individuals.[8]

In the present study, BMI of the patients and controls was similar at the time of recruitment of the study population at 5 years after acute NE. However, at 10 years, BMI was significantly higher in patients than controls. Although obesity is an important factor predisposing to the elevation of blood pressure, it does not explain the development of hypertension in controls between 5 and 10 years in this study, as their BMI remained stable. In the whole study population, hypertensive subjects were more obese than normotensive subjects, and BMI showed a direct association with both systolic and diastolic blood pressure.

Essential hypertension does not have a single cause, but kidneys seem to have an important role in its pathogenesis.[15] It has been proposed that renal microvascular disease, accompanied by interstitial inflammatory and tubular changes, plays a critical role in the genesis of hypertension.[16] Any factor causing renal vasoconstriction, especially in the outer medulla and the adjacent cortex, may induce this injury. Theoretically, hantavirus infection might act as an initiating factor for renal vasoconstriction. Autopsy studies have shown that the renal medulla is the most affected part of the kidney in hemorrhagic fever with renal syndrome.[17] The most characteristic histopathological lesions in renal biopsies of NE patients have been congestion and hemorrhage around the vessels in the outer medulla or corticomedullary junction with interstitial inflammatory cell infiltrates.[4,7,18] Increased expression of endothelial adhesion molecules, tumor necrosis factor-α, tumor growth factor-β, and platelet-derived growth factor has been detected to colocalize with the inflammatory cell infiltrates.[19] Hantaviruses seem to have a special predilection to infect vascular endothelial cells.[20,21]

The glomerular hyperfiltration of the patients, detected at 5 years after NE, had subsided at 10 years, whereas the GFR of the controls remained stable throughout the study. Consequently, no difference in GFR was detected between the patient and the control groups at 10 years. Glomerular hyperfiltration is most widely known as a feature of early diabetic nephropathy.[22,23] There is also some evidence of glomerular hyperfiltration in adult polycystic kidney disease,[24] as well as in essential hypertension.[25] However, to our knowledge, there are no previous reports of glomerular hyperfiltration after acute tubulointerstitial nephritides. It seems plausible that distinct pathophysiological mechanisms could underlie the increases in GFR under different disorders. In this study, the underlying mechanisms of glomerular hyperfiltration at 5 years after NE cannot be determined from the available set of data, although one possibility is that this could be a secondary phenomenon to the elevated systolic blood pressure. It remains to be investigated whether the GFR of NE patients will remain normal or show accelerated decline during a still longer follow-up.

In the present study, mild functional tubular defects were detected 1–6 years after acute NE, in concert with earlier studies.[4,12,26,27] The mild proteinuria, especially elevated urinary α1-microglobulin excretion that reflects tubular dysfunction, also disappeared within 10 years after acute NE. Altogether, it is noteworthy that the present patients showed concurrent increases in blood pressure, GFR, and urinary protein excretion at 5 years after acute NE, whereas none of these variables differed from those in the healthy controls at 10 years after acute NE.

In summary, the 10-year prognosis after acute NE seems to be favorable, although NE may predispose some patients to the development hypertension. It is not known whether the glomerular hyperfiltration, observed 5 years after acute NE in some patients, is an early sign of renal injury that could eventually lead to a decline of GFR. Further follow-up will be needed to establish the final outcome.

MATERIALS AND METHODS

Study population and protocol

Originally, there were 46 patients and 38 controls in the study concerning the 5-year prognosis of acute NE.[9] Of them, 10 years after NE, we were able to re-examine 36 patients (20 males and 16 females) aged from 32 to 68 (mean 50) years and 29 controls (14 males and 15 females) aged from 30 to 69 (mean 51) years. The patients had been originally hospitalized owing to serologically verified NE[28] during the years 1990–1995 at the Department of Internal Medicine, Tampere University Hospital. They were examined 3–7 (mean 5)[9] and 8–13 (mean 10) years after acute NE. The controls were recruited by an open announcement as described previously.[9] At 5 years, the patient and control groups were comparable to each other with respect to age, gender, and BMI. A detailed clinical survey of all subjects was carried out on an outpatient basis from February to May 2003 at Tampere University Hospital.

The following diseases before NE were recorded in five patients: ankylosing spondylarthritis in two, and coronary heart disease,

bronchial asthma, and chronic schizophrenia in one each. The patient with asthma had also hypothyroidism. One of the controls had hypothyroidism. All these subjects continued to use their regular medication over the study period.

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

Laboratory specimens and electrocardiogram

Blood specimens were obtained in the morning after a minimum 12-h fast. During the years 1990–1995, serum creatinine, urea, cholesterol, triglycerides, and blood glucose were analyzed by Vitros (Johnson & Johnson, Rochester, NY, USA) and in 2003 by Cobas Integra Analyzer (F Hoffmann-LaRoche Ltd, Basel, Switzerland). Serum creatinine concentrations that were determined in 2003 showed 10% lower values than those analyzed during the years 1990–1995 owing to above change of the determination method. Blood cell count was determined by H2 or H3 hematological analyzer (Bayer Corporation, Tarrytown, NY, USA) and blood hemoglobin A1c by Roche Diagnostics (Mannheim, Germany). Negative Puumala virus serology of the controls was confirmed.[28]

The 24-h, nightly and daytime urinary protein excretion, and the overnight urinary excretion of α1-microglobulin, albumin, and immunoglobulin G were measured. The spot samples of morning urine were collected after a minimum of 12 h of fasting and analyzed for osmolality, erythrocytes, leukocytes, albumin, nitrite, glucose, pH, and ketones. Osmolality of urine was measured by the Advanced Cryomatic™ Osmometer (Advanced Instruments Inc., Needham Heights, MA, USA). Hematuria was defined as a positive dipstick test for erythrocytes and over two erythrocytes per high-power field. Overnight urinary excretion of α1-microglobulin $\geqslant 7\,\mu g/min$, albumin $\geqslant 11\,\mu g/min$, and immunoglobulin G $\geqslant 5\,\mu g/min$ were considered abnormal, based on the healthy reference material of our laboratory.[9]

Electrocardiograms were evaluated according to the Minnesota codes. Left ventricular mass was evaluated by the sum of the height of the S-wave in lead V1 (SV1) and the R-wave in lead V5 (RV5) of a 12-lead resting ECG. BMI was calculated by dividing weight (kg) by the square of height (m^2).

Determination of renal function

GFR was determined by the single injection method as a plasma clearance of ^{51}Cr-ethylenediaminetetraacetic acid after a light meal and expressed in values normalized for body surface area. Effective renal plasma flow was estimated by clearance of ^{131}I-hippurate. The filtration fraction was calculated as the quotient of GFR and effective renal plasma flow. Two patients at 5 years refused these examinations. At 10 years, GFR and effective renal plasma flow were not determined in one patient and one control owing to pregnancy.

Blood pressure monitoring

The ABP was measured with a fully automatic recorder. The cutoff point that defined hypertension was a 24-h mean ABP $\geqslant$133/82 mm Hg according to a large population study.[11] Office blood pressure was also measured, and the cutoff point for hypertension was $\geqslant$140/90 mm Hg according to the WHO/ISH guidelines.[29] We defined patients as hypertensives if they were on antihypertensive therapy, or had mean ABP $\geqslant$133/82 mm Hg, or had office blood pressure $\geqslant$140/90 mm Hg. Office blood pressure was used to define hypertension only if ABP monitoring was not determined.

Statistical analysis

To describe the data, means and s.d. are given for normally distributed variables, and medians and ranges for skew-distributed continuous variables. Groups were compared using independent sample *t*-tests for normally distributed variables, and Mann–Whitney *U*-tests for skewed variables. Categorical data were analyzed by χ^2 test or by Fisher's exact test. The results of 5- and 10-year prognosis of NE were compared with paired-samples *t*-test for normally distributed variables, and with Wilcoxon's matched pairs signed rank-sum test for skewed variables. Associations between BMI and blood pressure, and BMI and blood glucose were analyzed using Pearson's correlation. All tests were two sided and analyses were performed with the SPSS for Windows version 13 (SPSS Inc., Chicago, IL, USA).

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