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The Risk of Developing Endemic Nephropathy in Subjects with Proteinuria

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A B S T R A C T

Endemic nephropathy is a chronic tubulointerstitial disease characterized by early damage to the proximal tubule, with low-molecular weight proteinuria being an important hallmark and possible tool for early diagnosis. The aim of this retrospective cohort study was to assess the risk of developing endemic nephropathy in subjects with proteinuria from the endemic region in Croatia. The cohort study included subjects with proteinuria determined by the sulfosalicylic acid method (after 1988 with strip method), involved in the field survey conducted in the Croatian endemic village of Kaniža in 1975 and followed up until 1997. Subjects with endemic nephropathy established at the first visit and patients that failed to present for follow up visits after 1975. were excluded. In the field survey group that consisted of 624 subjects (286 male and 338 female), proteinuria was established in 157 subjects. Upon the application of exclusion and inclusion criteria, the study cohort included 111 of 157 subjects. The mean follow up was 7.26 years (95% confidence interval 4.06–10.46 years). During the follow up period, 19 (17%) subjects with initial proteinuria developed endemic nephropathy. The incidence density of endemic nephropathy among subjects with proteinuria was 1.3 per 100 persons/year. Estimated risk was 0.0137 (confidence interval 0.0087–0.0214) per year of exposure. The presence of proteinuria determined by the sulfosalicylic acid or test strip in subjects from the endemic village indicated that endemic nephropathy would develop in 1.3 of 100 subjects with proteinuria per year.

***Key words**: chronic kidney disease, endemic nephropathy, incidence density, proteinuria*

Introduction

Endemic (Balkan) nephropathy (EN) is a chronic tubulointerstitial disease with insidious onset and a slow but progressive clinical course eventually leading to chronic renal failure[1,2]. EN has been recorded only in farming villages located near big tributaries of the Danube River in Bosnia and Herzegovina, Bulgaria, Croatia, Romania and Serbia. In Croatia, it has been found in 14 villages to the west of Slavonski Brod, which is situated in the eastern part of inland Croatia[1].

EN is also strongly associated with upper urothelial cancers. In the endemic area, the specific mortality rate of upper urothelial cancer has been 55-fold that recorded at the national level[3]. An increased mortality rate of upper urothelial cancers in endemic *versus* non-endemic areas has also been reported from other countries[4]. Over years, numerous etiologic hypotheses including mycotoxins, infectious agents, heavy metals and genetic predisposition have been investigated[5–10]. Most recently, the results reported by a Croatian/US team of investigators have pointed to aristolochic acid from *Aristolochia clematitis* as the etiologic factor for EN, with the possible genetic factors involved in the respective susceptibility[5,11–14].

The first epidemiological field survey in the Croatian endemic area was conducted in 1957 in the villages of Pričac and Bebrina[15]. Since that time, field surveys have been carried out periodically in endemic and a few non-endemic villages. In the endemic village of Kaniža, survey was conducted continuously from 1975 to 1997, and was interrupted only in 1992 due to the war in Croatia. Surveys were much less frequently performed in other villages of the Croatian endemic area, with just a single survey being carried out in some villages[15,16].

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The World Health Organization (WHO) established diagnostic criteria for the diagnosis of EN and classification of the population at risk[17]. These criteria have been validated and refined by several research groups in order to enable more precise diagnosis of the disease early in its course[18–20].

There is no specific diagnostic marker of EN. Urine analysis is very important in the diagnosis of EN. Proteinuria is one of the major EN features and an essential diagnostic marker. In the last few decades, proteinuria has been defined as low-molecular weight tubular proteinuria due to an early proximal tubule lesion. In the early stage of the disease, proteinuria is mild, intermittent, and characterized by excretion of low-molecular weight protein. This was recognized even in the first surveys carried out in the 1960s, when proteinuira was determined by the sulfosalicylic acid method and later by use of test strip. Significantly higher rates of proteinuria have been found in the population living in the endemic area as compared with those living out of endemic villages[21–24].

Although proteinuria is an important component of the disease, and suggested as a possible early marker of EN, the risk of developing EN in individuals with proteinuria identified by screening testing has not yet been evaluated. EN develops in some but not all patients with proteinuria from the Croatian endemic area. Thus, the aim of this study was to assess the risk of developing EN in subjects with proteinuria living in an endemic area.

Subjects and Methods

This retrospective cohort study included subjects involved in the field study carried out in the Croatian endemic village of Kaniža in 1975. A total of 624 subjects were followed-up yearly until 1997, with the exception of 1992 due to the war in Croatia. Systematic annual surveys in the village of Kaniža have not been performed since 1997. In the 1975 field survey, all inhabitants older than 3 years were invited to participate in the door-to--door survey. The data collected were stored at the Public Health Institute of the Brod-Posavina County in Slavonski Brod, containing the following information: family/household history of EN, personal history of chronic diseases, occupation, year of birth, sex, period living in endemic area, proteinuria, serum creatinine and hemoglobin levels. According to the modified WHO criteria, currently used in Croatia, the following diagnostic markers for subjects living in an endemic area were used: (a) positive family/household history of EN; (b) low weight proteinuria; (c) serum creatinine concentration >132.7 μmol/L; (d) anemia (Hb <120 g/L in men and Hb <113 g/L in women); and (e) exclusion of all other chronic renal diseases. Using these markers, subjects are classified into one of five groups as follows: group 1 – established EN includes the following marker combinations: a+b+ +c+d+e, or b+c+d+e, or a+b+d+e; group 2 – suspect of having EN includes the following marker combinations: a+b+e, or b+d+e; group 3 – subjects at risk of having EN have the following marker: a; group 4 – subjects free from EN are negative for the following markers: a, b, c and d; and group 5 – unclassified.

Proteinuria was determined by the method of sulfosalicylic acid (>0.2 g/L) until 1987, and by test strip (>0.3 g/L) (Urocomb 9, Pliva, Zagreb, Croatia) from 1988 to 1997. The inclusion criterion for this analysis was positive screening test for proteinuria at the beginning of follow up in 1975. Out of 624 subjects, 157 were positive for proteinuria. Subjects with established EN at baseline were excluded. Out of 157 subjects positive for proteinuria, 37 subjects met the WHO criteria for EN at the beginning of the follow up period. Nine subjects that failed to present for follow up examinations after 1975 were also excluded irrespective of the reason; thus, the study cohort included 111 subjects. They were followed-up from 1975 to the time of EN development, withdrawal from the study, or study completion in 1997.

Statistics

Because of different follow up period for each subject in the study cohort, incidence density was used to calculate the risk of developing EN in subjects with proteinuria at baseline. Incidence density (ID) was calculated according to the equation: Risk = 1–exp (–ID x follow up period), where ID is incidence density in person/year[25]. With the assumption that the rate is constant over time, the risk is calculated with the corresponding 95% confidence interval (CI). As time to the onset of EN varied during follow up of patients with proteinuria, the risk could not be calculated directly but had to be assessed by use of incidence density.

Results

Basic demographic characteristics of study subjects with proteinuria are shown in Tables 1 and 2.

The 1975 field study included 624 subjects (286 male and 338 female) of 884 inhabitants then living in the village, yielding a 70.6% rate of response. The prevalence of proteinuria was 25%. In 1975, the diagnosis of EN according to the WHO criteria was made in 37 subjects; thus, the prevalence of EN in the village of Kaniža was 5.9%. Upon exclusion of subjects with established EN and those that did not present for follow up examinations after 1975, there were 111 subjects with proteinuria. According to the WHO criteria, 19 of these 111 subjects developed EN during the follow up period (arithmetic mean 7.26 years; 95% CI 4.06–10.46 years). Nineteen of 111 study subjects with proteinuria were followed up for 1378 years in total before developing EN, yielding the incidence density of EN; the incidence of subjects with proteinuria was 1.3 *per* 100 persons/year.

The risk of developing EN within a certain time in subjects positive for proteinuria and living in the endemic area with corresponding 95% CI is shown in Table 3 and Figure 1.

TABLE 1
BASIC DEMOGRAPHIC CHARACTERISTICS OF STUDY COHORT (SUBJECTS WITH PROTEINURIA)

		Endemic nephropathy developed during follow up				Total	
		Yes		No			
		n	%	n	%	n	%
Gender	Male	6	5.4	43	38.7	49	44.1
	Female	13	11.7	49	44.1	62	55.9
Place of birth	Endemic village	16	14.4	64	57.7	80	72.1
	Elsewhere	3	2.7	28	25.2	31	27.9
Family history of endemic nephropathy	Positive	5	4.5	33	29.7	38	34.2
	Negative	14	12.6	59	53.2	73	65.8

TABLE 2
EPIDEMIOLOGICAL CHARACTERISTICS OF SUBJECTS WITH PROTEINURIA INCLUDED IN FOLLOW UP

		Endemic nephropathy developed during follow up	
		Yes	No
Age (yrs)	$\overline{X}$	51	39.3
	Standard deviation	14.77	22.97
	95% CI	44–58	35–44
	Median	52	40.5
	Range	14–76	8–92
Age at endemic nephropathy diagnosis or follow up completion (yrs)	$\overline{X}$	58.3	52.8
	Standard deviation	14.62	22.28
	95% CI	51–65	48–57
	Median	60	57.5
	Range	17–78	11–97

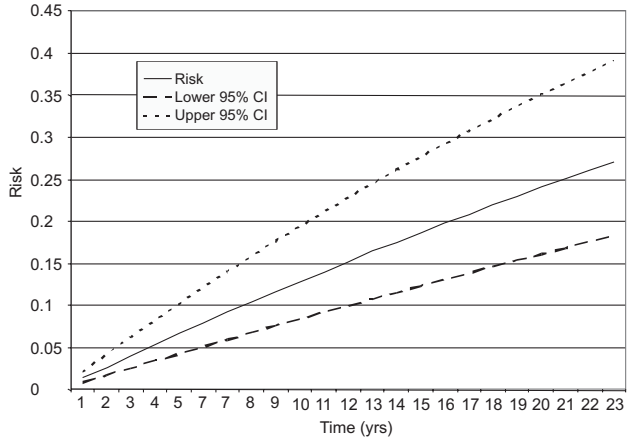

Fig. 1. Risk of developing endemic nephropathy in subjects with proteinuria and respective 95% confidence interval (CI).

Discussion

Field studies regularly carried out annually in the Croatian endemic area covered only the village of Kaniža during the 1975–1997 period, with the only interruption in 1992 due to the war in Croatia. During that period, only one field survey was carried out in some villages (Zbjeg, Živike and Dubočac) to nine surveys having been conducted in the village of Bebrina[1,26,27]. Since 1997, only one field survey was carried out in the endemic village of Kaniža, in 2005[28]. Epidemiological characteristics of study patients did not differ substantially from other literature reports[28–32]. Interestingly, in our study cohort we identified a subject who developed EN at the age of 17, and another one who developed EN after 10 years spent in the EN area.

Another interesting observation was age difference between the EN group and group of subjects that did not develop EN during follow up period. Reason for this could be that children were also recruited in the 1975 field survey. The possible reasons for some people having refused to take part in the field survey could be joining the army, work out of Kaniža, etc. According to literature reports, more women then men develop EN[33,34].

The highest prevalence of EN of 8.3% was recorded in the endemic village of Pričac in 1977[1]. In the village of Kaniža, the prevalence of EN ranged from 4.4% in 1975 to 0.6% in 2005[1,28]. During the 1975–1997 period, the annual incidence of EN ranged from 4.9‰ in 1997 to 0‰ in

TABLE 3
RISK OF DEVELOPING ENDEMIC NEPHROPATHY IN SUBJECTS WITH PROTEINURIA AND RESPECTIVE 95% CONFIDENCE INTERVAL (CI)

Time of exposure (yrs)	Risk	Lower 95% CI	Upper 95% CI
1	0.0137	0.0087	0.0214
2	0.0272	0.0174	0.0423
3	0.0405	0.0260	0.0628
4	0.0536	0.0346	0.0828
5	0.0666	0.0430	0.1024
6	0.0794	0.0514	0.1216
7	0.0920	0.0597	0.1404
8	0.1044	0.0679	0.1588
9	0.1167	0.0761	0.1768
10	0.1288	0.0842	0.1944
11	0.1407	0.0922	0.2116
12	0.1525	0.1001	0.2284
13	0.1641	0.1080	0.2450
14	0.1755	0.1158	0.2611
15	0.1868	0.1235	0.2769
16	0.1980	0.1313	0.2924
17	0.2089	0.1389	0.3075
18	0.2198	0.1464	0.3223
19	0.2304	0.1539	0.3368
20	0.2410	0.1613	0.3510
21	0.2514	0.1686	0.3649
22	0.2616	0.1759	0.3785
23	0.2718	0.1831	0.3917

1985[16,28]. In this study, the prevalence of proteinuria was 25% in 1975, whereas the reported prevalence of proteinuria determined by the sulfosalicylic acid method in the endemic area in Serbia was 15.9%[35]. Determination of proteinuria using sulfosalicylic acid and test strip as a nonspecific method was a limitation of the present study. However, this method had for years been used not only as a basic screening method, but as one of diagnostic criteria. In the last several decades, more precise markers of proximal tubular damage have been developed and used in Croatia since the early 1990s. Positive finding of proteinuria is defined as $beta_2$-microglobulinuria >0.3 mg/L and $alpha_1$-microglobulinuria >10 mg/L[21].

To the best of our knowledge, there are no literature reports on such an approach in assessing the risk of developing EN in patients with proteinuria. In the present study, regular annual field surveys carried out in a single endemic village in Croatia over a 23-year period were analyzed. Despite relatively small population of EN cases, and evidence that prevalence of EN in the endemic Croatian areas appears to be decreasing[28,30] assessing the risk of EN with the assumption that the rate is constant over time has yielded valuable information for planning public health actions, and indicating the need of additional field surveys to clarify possible risk changes over time.

In the village of Kaniža, the EN incidence density in individuals with proteinuria was 1.3 *per* 100 individuals with proteinuria *per* year. Very few studies report incidence density or other measures of risk of EN. However, studies conducted in Serbia report the mortality rates with or from EN during the 1974–1988 period to be 3.3 *per* 1000 persons/year and incidence rate of upper urothelial tumors 1.4 *per* 1000 persons/year[36,37]. Patients with $beta_2$-microglobulinuria have a 9.9-fold relative risk of EN development recorded in subjects without $beta_2$--microglobulinuria[36]. In our study, the risk increased with the years of living in the endemic area (Fig. 1). In another study, 10 of 48 subjects (20.8%) with $beta_2$-microglobulinuria and 17% of subjects with proteinuria developed EN[38]. However, the results obtained in this study showed that 1.3 subjects *per* 100 individuals with proteinuria established by the sulfosalicylic acid method developed EN *per* year.

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RIZIK RAZVOJA ENDEMSKE NEFROPATIJE U OSOBA S PROTEINURIJOM U ENDEMSKOM PODRUČJU

S A Ž E T A K

Endemska nefropatija je kronična tubulointersticijska bolest karakterizirana oštećenjem proksimalnog tubula. Proteinurija je važan dijagnostički znak i mogući biljeg za ranu dijagnozu. Cilj ove retrospektivne studije je prikazati rizik razvoja endemske nefropatije kod osoba s proteinurijom u endemskom području u Hrvatskoj. U studiju su uključene sve osobe s proteinurijom utvrđenom sulfosalicilnom kiselinom pri terenskom istraživanju u endemskom selu Kaniža 1975. godine. Te osobe su praćene do 1997.godine. Osobe s proteinurijom koje su 1975. godine imale endemsku nefropatiju su isključene kao i one koje se nisu kasnije javljale na pregled. Proteinurija je utvrđena u 157 od 624 osobe pri prvom pregledu u endemskom selu Kaniža. Nakon primjene isključujućih kriterija ostalo je od 157 osoba s proteinurijom, 111 osoba koji su prosječno praćeni 7,26 godina (95% CI 4,06–10,46 godina). Za vrijeme perioda praćenja kod 19 (17%) osoba se razvila endemska nefropatija. Procijenjeni rizik je bio 0.0137 (CI 0,0087–0,0214) za svaku godinu izloženosti. U osoba s proteinurijom utvrđenom sulfosalicilnom kiselinom u endemskim selima endemska nefropatija se razvije u 1,3 osobu od 100 osoba s proteinurijom godišnje.