Kidney & Blood Pressure Research

Could Disappearance of Endemic (Balkan) Nephropathy Be Expected in Forthcoming Decades?

Ante Cvitković[a]   Ivana Vuković-Lela[b]   Karen L. Edwards[d]   Sandra Karanović[b]
Dragana Jurić[a]   Dubravka Čvorišćec[c]   Mirjana Fuček[c]   Bojan Jelaković[b]

[a]Institute for Public Health, County Brodsko Posavska, Slavonski Brod, [b]Department of Nephrology, Arterial Hypertension and Dialysis, School of Medicine, University of Zagreb, and [c]Laboratory for Clinical Diagnosis, University Hospital Center, Zagreb, Croatia; [d]Department of Epidemiology, University of Washington, Seattle, Wash., USA

Abstract
Background/Aims: An epidemiological survey of endemic nephropathy (EN) was performed in endemic Croatian areas and the current prevalence was compared to that reported for the same villages several decades ago. *Methods:* A total of 2,487 adult farmers from 6 endemic villages and 3 non-endemic villages were enrolled. An extensive epidemiological questionnaire, clinical examination and laboratory analyses of blood and urine were performed. According to the modified WHO criteria, participants were classified into diseased, suspected of having EN, and those at risk of developing EN. *Results:* The overall prevalence of EN in the Croatian areas was 1.0%, ranging between 0.3 and 2.3% in different villages. Those suspected of having EN amounted to 3.9%. In the endemic villages a decreasing trend in the prevalence of EN was observed comparable to the results obtained in previous surveys. It is interesting to note that no EN patients were recorded in the endemic village of Dubočac. *Conclusion:* The prevalence of EN in the endemic Croatian areas appears to be decreasing. For the first time, we failed to detect any EN patients in a village that was previously considered endemic, which might indicate that EN is diminishing.

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Introduction

Endemic nephropathy (EN) is chronic tubulointerstitial nephritis with an insidious start and slowly progressive course leading to chronic kidney failure. EN affects a rural population in Bosnia and Herzegovina, Bulgaria, Croatia, Romania, and Serbia. EN cases were recorded in several households, but without a hereditary pattern. Endemic focus in Croatia comprises 14 villages situated near the city of Slavonski Brod in a once inundated and in the past often flooded valley [1, 2]. According to the census from 2001, the endangered population was 10,865 [3]. Over a 45-year period (1957–2002) EN was the cause of

Prof. Bojan Jelaković, MD, PhD
School of Medicine, University of Zagreb
Šalata 3
HR–10000 Zagreb (Croatia)
Tel. +385 1 238 8271, E-Mail jelakovicbojan@gmail.com

death for 626 inhabitants from endemic villages [1, 2]. EN is strongly associated with upper urinary tract transitional cell (urothelial) cancers (UUCs) [1, 2, 4]. Specific mortality from UUC in endemic areas is 55 times higher than in the non-endemic parts of Croatia. A high mortality rate from UUC in endemic areas was reported in several Balkan countries [2, 4, 5]. Numerous hypotheses regarding the etiology of EN and incriminating environmental agents including mycotoxins (ochratoxin A), heavy metals, trace metal deficiencies, and polycyclic aromatic hydrocarbons from coal deposits *(Pliocene lignite)* have been put forward [6–8]. Recently, chronic ingestion of aristolochic acid, a component of *Aristolochia clematitis,* was shown to be the causative agent of both chronic tubulointerstitial nephritis and UUC [8–13], thus EN should be considered an environmental form of aristolochic acid nephropathy [12, 14, 15].

The first systematic field research with an endemic focus on Croatia was conducted in 1957 and, thereafter, research examinations of the endangered population of the endemic villages have continued in order to reveal the etiological agent but also to determine early diagnostic markers and an optimal therapeutic approach enabling us to follow the clinical and epidemiological course of EN and to compare data obtained in the past with results from recent surveys.

According to some authors the prevalence of EN in other endemic areas has remained stable over time and at the same level as it was several decades ago, while others have reported that it was on a significant decrease [16–22].

Our aim was to determine the current prevalence of EN in 6 endemic Croatian villages and to compare it with the results obtained in epidemiological studies performed in the same villages several decades ago.

Subjects and Methods

A total of 2,487 inhabitants from the endemic villages of Slavonski Kobaš, Živike, Pričac, Šumeće, Dubočac and Zbjeg, and the non-endemic villages of Klakar, Donja Bebrina and Rastušje were enrolled in a survey conducted between 2008 and 2010. All adult farmers from those villages were informed in detail and invited to participate on a door-to-door basis. Prior to examination, informed consent was obtained from each participant. After taking a full medical history (including an extended epidemiological questionnaire) and performing a physical examination, fasting blood was drawn and a morning urine specimen was taken. All laboratory analyses were performed in the Laboratory for Clinical Diagnosis, University Hospital Center Zagreb. Urinary α1-microglobulin and albumin concentrations were determined using an immunonephelometric assay (latex-enhanced nephelometry) on a Behring Nephelometer II (Behring Diagnostics GmbH, Marburg, Germany). Values were normalized to urine creatinine. Hemoglobin was determined by electronic counter Cell Dyn 1800. Serum and urine creatinine concentrations were measured by 'continuous' photometry with alkyl pikrat on Olympus AU 2700. The study was approved by the Ethical Boards of the School of Medicine, University of Zagreb, the Croatian National Institute of Public Health and General Hospital 'Dr. Josip Benčević', Slavonski Brod.

The different criteria used across various countries to establish a diagnosis of EN and to classify the endangered population make an exact comparison of the EN prevalence between different endemic areas difficult to achieve [16, 18, 20, 23–28]. In Croatia, the modified WHO criteria have been used for the last 4 decades. Although all these criteria have some serious drawbacks, we have applied them in this study because our aim was to compare the prevalence reported here with results obtained in the past. The modified WHO criteria classify subjects into 4 groups: 'diseased', 'suspected' of having EN, 'at risk' of having EN, and 'others', based on the following diagnostic data: (a) positive family/household history of EN; (b) low molecular weight proteinuria (α1-microglobulin >10 mg/l or α1-microglobulin/creatinine >14 mg/g); (c) serum creatinine >132.6 μmol/l; (d) anemia (hemoglobin<120 g/l if male, Hb <113 g/l if female), and (e) exclusion of other renal diseases (including diabetes). Subjects were considered 'diseased' if they were positive for 'a+b+c+d+e', or 'b+c+d+e', or 'a+b+d+e'; 'suspected' if they had 'a+b' or 'b+d'; 'at risk' if they were from family/household with EN, and 'others' if they did not comply with any of the above requirements. Routine laboratory tests, imagining techniques (ultrasound, MSCT or MRI) and kidney biopsy were used in order to exclude other types of kidney disease when necessary.

All data were entered into the database and statistical analyses were performed using STATISTICA software, version 9.1. Clinical and laboratory data are reported as the frequency of categorical parameters and as the mean and standard deviation (SD) of continuous variables. Data of subgroups were compared using one-way analysis of variance (ANOVA) for continuous variables with normal distribution and MANOVA for variables with non-normal distribution. Statistical significance between the subgroups was determined using the χ^2 test for discrete variables, and $p < 0.05$ was considered significant. The number of inhabitants from every village was determined according to the census of 2001. The prevalence of EN patients was calculated and expressed as a percentage of the total number of eligible inhabitants of endemic villages.

Results

The overall participation rate in this survey was 91% of the eligible adult inhabitants. These 6 villages represent 42.8% of the villages in endemic areas in Croatia. A diagnosis of EN was established in 33 subjects (14 males, 19 females), and as shown in table 1 the overall prevalence of EN is 1.0%, and 130 participants (3.9%) were classified

Table 1. Prevalence of diseased subjects, those with suspected EN, and those at risk of EN

Village	Total number of inhabitants[1]	Enrolled farmers n (%)	Diseased n (%)	Suspected EN n (%)	At risk of EN n (%)
Slavonski Kobaš	1,303	751 (57.6)	24 (1.8)	85 (6.5)	165 (12.7)
Živike	308	125 (40.6)	1 (0.3)	10 (3.2)	18 (5.8)
Pričac	132	63 (47.7)	3 (2.3)	6 (4.5)	13 (9.8)
Šumeće	610	435 (71.3)	3 (0.5)	12 (1.9)	39 (6.4)
Dubočac	282	177 (62.8)	0	5 (1.8)	15 (5.3)
Zbjeg	510	343 (67.3)	2 (0.4)	5 (0.9)	17 (3.3)
Total EN villages	3,145	1,894 (60.2)	33 (1.0)	123 (3.9)	267 (8.5)
Klakar[2]	290	149 (51.4)	0	1 (0.3)	0
Donja Bebrina[2]	469	228 (48.6)	0	5 (1.1)	2 (0.4)
Rastušje[2]	279	216 (77.4)	0	1 (0.4)	2 (0.7)

[1] According to 2001 census. [2] Control, non-endemic villages.

as suspects for EN (63 males, 67 females). Gender distribution was not significantly different between diseased subjects and those suspected of having EN versus those at risk of having EN as well as versus others (p = 0.062) and farmers from non-endemic villages (p = 0.191). Diseased subjects and those suspected of having EN were significantly older than those at risk, others and farmers from non-endemic villages (74.1 ± 7.7 and 59.9 ± 16.2 years of age vs. 47.2 ± 15.6, 50.3 ± 17.5, 53.3 ± 17.1 years of age, respectively; p < 0.0001) and consequently, they spent the longest period of life in their villages (70.8 ± 10.2 vs. 55.5 ± 19.3 years, 41.3 ± 17.4, 39.6 ± 21.2 and 42.5 ± 21.4 years, respectively; p < 0.0001). There were no differences in duration of living in the same village between those at risk, others and farmers from control villages (p = 0.051). None of the farmers from non-endemic villages was classified as diseased. However, we have identified 7 suspected (3 men, 4 women) and 4 at risk of developing EN (4 women) in non-endemic villages.

In endemic villages the prevalence of diseased subjects ranges between 0 and 2.3%. For the first time no farmer was found to have EN in 1 endemic village (Dubočac). The prevalence of suspected and those at risk in endemic villages ranges between 0.9 and 6.5% and 3.3 and 12.7%, respectively. In non-endemic villages, the prevalence of those suspected of having EN and those at risk ranges between 0.3 and 1.3% and 0 and 0.7%, respectively.

The prevalence of EN in endemic Croatian villages has decreased during the last 4 decades. In 1977, the highest prevalence rate of 8.3% was recorded in the village of Pričac. In this survey, the prevalence rate remained the highest in this village but it had decreased to 2.3%. A de-

creasing trend is present in all other endemic villages. In surveys performed in the 1970s and 1980s, the prevalence of disease was 2.4, 1.9, 0.8, 2.0 and 0.4% in the villages of Slavonski Kobaš, Šumeće, Zbjeg, Dubočac and Živike, respectively.

Discussion

For many decades, the prevalence of EN remained stable and approximately the same in the majority of endemic areas. However, over the past several years, diverse and even opposite data on prevalence have been reported in several countries harboring EN [3, 16–20, 22, 29]. This could suggest that disease activity differs between endemic foci implying that an environmental agent is still very present in some endemic areas, while decreasing or absent in others. Alternatively, the differences in prevalence observed in different countries could also be due to the use of different diagnostic criteria [24–28], differences in case fatality or duration of disease. In the past, the prevalence of EN in Croatia was in concordance with the majority of the results obtained in other endemic areas ranging between 0.4 and 8.3% [1, 3, 30] with an average of 4.9% (data on record in the Public Health Institute, Slavonski Brod). Since we aimed to compare recent results with data obtained several decades ago, and to present the dynamics of the prevalence trends over a period of time, we have applied the criteria used in the past being aware that present day diagnosis and classification of EN should be made using more reliable and more accurate diagnostic tools and cutoffs. The results of this survey

confirmed that EN has not disappeared and is still present in the endemic areas of Croatia. However, we have identified important new facts which should be taken into account when making projections and plans for healthcare in this area and also when discussing the etiology of this disease.

Firstly, we have observed a trend that suggests a decrease in the prevalence of confirmed cases of EN in the EN villages included in this survey which is in agreement with the reports of other authors [19, 20]. The same trend was observed for those suspected cases of EN. In our study, the prevalence of suspected EN cases ranged from 0.9 to 6.5%, while in studies conducted between 1976 and 1987 it ranged between 11.6 and 27.3% [31]. Our observation that the mean age has shifted to the older decades is again in accordance with other reports [16, 17, 31]. In the period 1960–1990 the average age of EN patients was 44.5 years and after 1990 the average age was 61.9 [3]. Women were slightly, but not significantly, more affected than men. The same was confirmed in this survey, again with a marked shift toward older age groups. Both facts indicate that the environmental agent is less active than in the past. The decreased prevalence could be due either to a decrease in incidence and/or that people with the disease are dying. The possibility that the prevalence has a decreasing trend due to case fatality could be ruled out because we and others [15, 16, 31] have observed a shift of the disease to older ages. So, in fact those with the disease or suspect of having EN are living longer today than in the past [2]. If exposure to the environmental agent has decreased or been eliminated, then it could be assumed that, over the next several decades, EN would disappear from this area. This presumption is supported by results obtained in the endemic village of Dubočac. In this endemic village, the EN prevalence of 2% in 1985 was higher than the overall prevalence of EN observed over the entire Croatian EN area in this most recent survey. However, in 2010, none of enrolled farmers from the village of Dubočac was diagnosed as an EN patient, and the number of suspected EN cases in this village was the smallest in the whole region. It is questionable whether this might be due to the fact that diseased subjects were not participating or those with EN died faster. However, all inhabitants were invited to participate, they all were examined in their homes and all members of previously identified positive EN families and households were enrolled. The participation rate was the same as in the surveys organized several decades ago when the same criteria were applied as in this study. The average age at death in this village is not different from other villages. As none of the diseased subjects moved out of this village, it is obvious that all EN patients from this village had died. Furthermore, a decrease in prevalence could not be explained by the diluting effect of immigrants from non-endemic areas. In the past 25 years only 30 immigrants have settled in this village (5 from non-endemic Bosnian villages, and 16 from non-endemic and 9 from endemic Croatian villages). In field survey we failed to diagnose any new case and, moreover, during the past 10 years none of the patients from the village of Dubočac starting dialysis has been diagnosed with EN (data on record from the General Hospital Slavonski Brod). Čukuranović et al. [19] found that the number of EN patients in the terminal phase as well as the number of EN patients with UUC is decreasing in south Serbia. This is in line with results from Bulgaria, and Dimitrov et al. [20, 22] raised the question whether EN would disappear. Gluhovschi et al. [18] reported that in recent years there have been no newly reported EN patients from the Caras-Severin foci in Romania. Recently, a group from Lazarevac, Serbia, reported that time trends in EN incidence suggest that the disease has not yet disappeared in the Kolubara region of Serbia [16]. They observed a nonsignificant increase in the period 1989–2009 and most a plausible explanation for this trend was given by the authors who commented that the increasing trend was a result of more vigorous screening and monitoring of EN over the last decade in comparison to the earlier period. Janković et al. [16] also found that in the youngest age group (20–44 years) the EN incidence rates were lower, but in the oldest age group (65+ years) significantly higher. These data are in concordance with our results on time trends of prevalence, and our conclusion that EN is still present, but new cases would only be diagnosed only in the elderly who in the past were exposed to the environmental risk factor for a long period of their lives. They had a slower clinical course and kidney damage became manifest in advanced ages. The difference among various endemic foci could result, as already mentioned, from the use of different diagnostic criteria, or might reflect differences in activity of the environmental toxic agent. Our recent studies clearly demonstrate that in Bosnia and Herzegovina, Croatia and Serbia, aristolochic acid is a causative agent [8–11, 13]. Information on the decreasing number of EN patients is important for public health authorities and for future projections as it could be presumed that the need for renal replacement therapy, at least due to EN, would be reduced in this region. Although the prevalence of EN is lower, a substantial number of diseased patients and those suspected of having EN is still present in the Croa-

tian endemic area. Screening of those at risk of developing EN and/or UUC, i.e. members of the households with registered cases, is still mandatory.

Secondly, we have detected several cases suspected of having EN and those at risk of developing EN in the villages outside a previously determined EN area. This is in line with the results of Nikolić et al. [32] who observed a higher UUC prevalence not only in the established Serbian endemic areas but also in the surrounding villages. The same was observed by other authors [29]. Very probably in the past, those cases were unrecognized. Thus, EN might have been under-diagnosed and some of the patients classified as unknown end-stage renal diseases in the national registries were in fact EN patients. This was a consequence of the established, almost dogmatic belief that EN could be diagnosed only in strongly restricted areas, and some diagnostic criteria even disable making a diagnosis of EN in such cases [28]. EN should be considered as part of the differential diagnosis in all rural patients classified as end-stage renal disease of unknown origin as well as in all UUC patients from rural areas not only in this part of Europe, but worldwide. However, this observation should be confirmed using more accurate diagnostic criteria.

Based on our results it can be concluded that EN is still present in the endemic area of Croatia and that screening of the endangered population is justifiable and necessary. Although this might seem inconsistent with our finding of a decrease in prevalence, it should be kept in mind that EN is characterized by slow onset. Regular examinations of those at risk who might develop the disease in forthcoming years are important regardless of whether or not they are currently exposed to the environmental agent.

The observed decrease in prevalence could indicate that the environmental agent is less active or even not active at all. This is in line with our previous results which showed that aristolochic acid is the main risk factor and causative agent of EN [8–11, 13, 15]. In the last few decades, exposure to this strong environmental nephrotoxin and carcinogen has decreased due to the significant improvement in farming and milling practices, disabling and preventing the contamination of flour. The decreased trend in prevalence and the shift in age of the diseased and suspected subjects to older ages indicate that further diminishing and even disappearance of EN could be expected within the next 15 years. Our finding of the presence of suspected EN cases in the established endemic area is also important as it raises an intriguing question as to whether some EN cases have been under-diagnosed in the past, thus contributing to underestimation of the true prevalence and distribution of disease. Today, EN should be excluded in all end-stage renal disease patients, particularly from rural areas, before being classified as an unknown renal disease.

Acknowledgements

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