

## BALKAN ENDEMIC NEPHROPATHY AND UPPER UROTHELIAL CANCER IN THE SOUTH MORAVA RIVER BASIN

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**Summary.** *The aim of this work was to establish the incidence, and trends in the last 30 years of Balkan endemic nephropathy (BEN) and upper urothelial cancer (UUC) appearing in the South Morava River basin settlements, in which BEN is an endemic disease. The data of 102 patients with BEN and 140 patients who were operated for UUC from 1969 to 1998, were analyzed. The patients originate from 17 settlements classified as endemic, hypoendemic, nonendemic (rural and city) based on BEN frequency in them. The results show decreasing trend of BEN and UUC appearing in endemic settlements. Also, the appearance of these disorders is more frequent among the older population groups, which is more expressed in BEN case. Significant familial association of these two disorders is evident. Demonstrated positive correlations in incidence and age structures in BEN and UUC people, and a family association of these disorders, give strong support to the speculations about their common etiopathogenesis.*

**Key words:** *Balkan endemic nephropathy, upper urothelial cancer, epidemiology*

### Introduction

After the second world war in the Balkans there is a more frequent appearance of chronic, tubulointerstitial kidney disease, bounded to well-defined areas along tributaries of the Danube River in Serbia, Bosnia, Croatia, Bulgaria and Romania, named Balkan endemic nephropathy (BEN) (1). This period is characterized by more frequent appearance of upper urothelial cancer (UUC) in the whole world, too (2,3). In the Balkans, it is far the expressed in areas where BEN is an endemic disease than in others. Explicitly, it relates to UUC (4,5,6). According to literature data, in the areas with BEN, UUC is more frequent, not only in general population (7,8,9,10), but also in families with BEN and patients with BEN (7,11,12,13,14).

An increased occurrence of urinary tract tumors in the South Morava River basin was first noted in 1964 (15). A significant conformity in territorial distribution of urinary tract tumors and BEN could be established (16,17,18). However, the nature of this appearance is not explained, yet. Since the etiology of these diseases is unknown, their unity is from the standpoint of eventually common etiopathogenesis actual problem nowadays. This is, before all, because the real dissemination and frequency of these diseases in most of affected areas have not been completely explored, yet.

The aim of this study was to establish the incidence

of BEN and UUC in the South Morava River basin during the last thirty years. There is evidence of decreasing of BEN incidence in this area (19).

### Patients and Methods

In the present study we reviewed 140 morphologically confirmed UUC, operated at the Clinic of Urology, Medical Faculty, Niš, in the period from 1969 to 1998. The tumors, diagnosed by the discovery of malignant cells in the urine and/or radiologically, which are not confirmed surgically including histological diagnosis, are not included in this study. Number, age and living place of patients with UUC were analysed for each year of analysing period. The patients originated from 15 village settlements and two cities of four communities in the South Morava River basin. On the basis of data from the Institute of Nephrology and Hemodialysis Clinical Centre, Niš, about BEN prevalence, all settlements are divided into four groups (20): 1) endemic, with more than 2% of the total population affected by BEN, 2) hypoendemic, with less than 2% of the population affected by BEN, 3) nonendemic village settlements, where the indigenous population was not affected by BEN and 4) nonendemic city settlements, where the indigenous population wasn't affected, either. Two last groups were the control settlements.

The incidence of BEN was estimated on the basis of the number of patients in the terminal stage of chronic

renal failure (CRF), who started cure by dialysis during every year in period from 1973 to 1998. Diagnosis of BEN was based on generally accepted clinico-epidemiologic and morphologic criteria (21).

The trend lines for these diseases were constructed from data on the number of patients with UUC and BEN for each year of analysed period. Data on patients' age made possible a graphic presentation of their age structure.

### Results

There were 140 cases of UUC registered on the territory with BEN in the South Morava River basin during the period from 1969 to 1998, and 102 BEN cases, from 1973 to 1998 in the terminal chronic renal failure stage.

The frequency of UUC in four group settlements in the South Morava River basin, during the period from 1969 to 1998, is presented in Table 1. Decreasing number of upper urothelial tumor was noted in hypoendemic and endemic settlements especially. A light increase of ill people was registered in nonendemic rural settlements, and a significant increase of incidence was noted in city settlements, especially during the second half of this period.

Table 1. Frequency of UUC in four group settlements in the South Morava River basin, during the period from 1969 to 1998

Year	Settlements				Total
	Endemic	Hypoendemic	Non-endemic rural	Non-endemic city	
1969	5	0	1	0	6
1970	2	1	0	0	3
1971	0	0	1	1	2
1972	0	0	1	2	3
1973	3	0	1	0	4
1974	0	2	0	0	2
1975	4	1	0	2	7
1976	0	1	1	2	4
1977	1	0	0	2	3
1978	0	2	1	1	4
1979	2	1	0	2	5
1980	0	1	0	0	1
1981	1	0	1	1	3
1982	1	0	2	0	3
1983	1	0	1	0	2
1984	2	0	2	1	5
1985	0	0	3	1	4
1986	0	0	0	7	7
1987	0	0	0	1	1
1988	0	0	0	9	9
1989	3	1	1	2	7
1990	1	1	2	9	13
1991	0	0	0	3	3
1992	0	0	2	2	4
1993	2	0	1	5	8
1994	0	1	1	4	6
1995	0	1	1	4	6
1996	2	0	1	5	8
1997	1	1	2	1	5
1998	0	0	0	2	2
Total	31	14	25	69	140

Trends of UUC incidence during the observed period are presented in Figure 1. The UUC occurrence in hypoendemic and endemic settlements shows a constant decreasing trend. The incidence of UUC shows light in nonendemic rural settlements, and considerable, in nonendemic city settlements, increase during the whole period. Finally, the incidence of UUC for the whole observed region, disregarding the type of settlement, was rising.

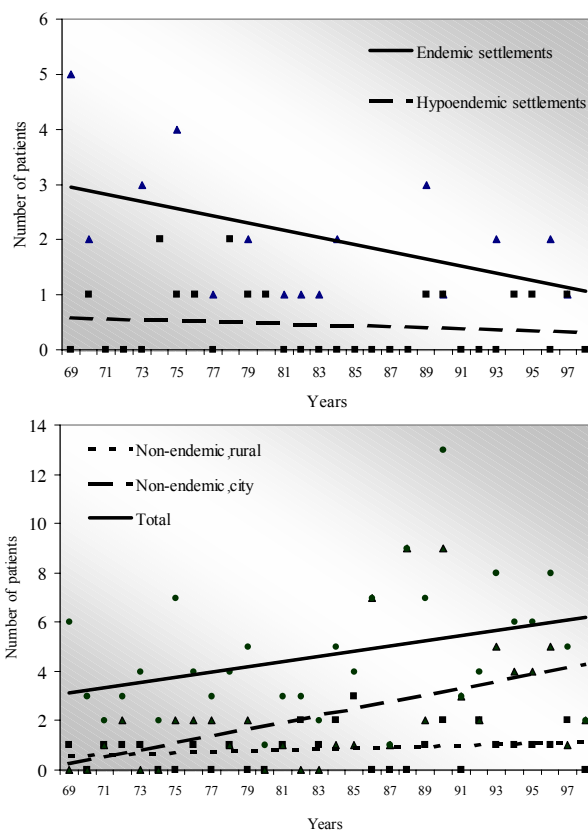


Fig. 1. Trend of UUC around the South Morava River from 1969 to 1998. Upper panel: endemic and hypoendemic settlements; lower panel: control settlements.

Figure 2 shows the decreasing trends of BEN and UUC in endemic settlements, for the period from 1973 to 1998. A more decreasing trend of BEN is evident.

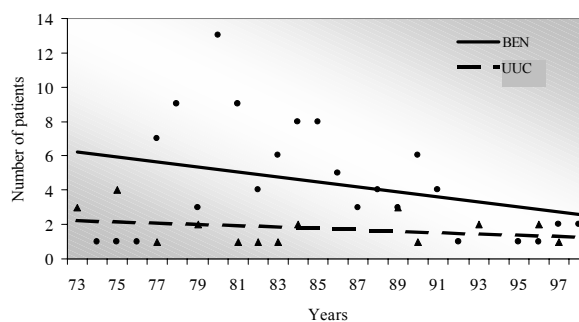


Fig. 2. Trend of BEN and UUC in endemic settlements around the South Morava River

Figure 3 shows the average age of BEN and UUC patients in endemic settlements for the observed period. It is obvious that the average age of BEN patients in the terminal stage of CRF moves to older age groups. It is also evident that the movement of average age of UUC patients to older age groups during the thirty years period is less expressed than in BEN cases.

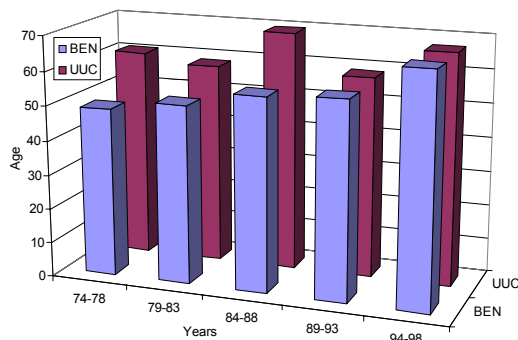


Fig. 3. Mean age of patients with BEN and UUC in endemic settlements around the South Morava River

Table 2 shows the frequency of UUC in families with BEN. There were registered 24 UUC cases in two endemic settlements with 711 families. There were 89 (12.5%) families affected with BEN, while there wasn't BEN in the remaining 622 (87.5%) families in the observed settlements. Upper urothelial tumors were found in 10 (11.23%) of 89 families with BEN, and in 14 (2.25%) of 622 families without BEN. Family occurrence of these tumors was 44 times less frequent in control settlements than in families with BEN, or relative risk (RR) for the UUC tumors in families with BEN is 44.53 in the most approximate terms.

Table 2. Frequency of UUC in families with BEN

Settlement-group	Number of families	UUC	
		Number	%
Endemic-families with BEN	89	10	11.23
Endemic-families free of BEN	622	14	2.25
Non-endemic-villages	2741	7	0.25
Non-endemic-large cities	52660	35	0.07

## Discussion

Despite the fact, that from the first observations about the increased incidence of the urinary tract tumors in some settlements around the South Morava River and its tributaries, almost four decades passed (15), the real occurrence of this phenomenon is still not well known. The reason for this is, first of all, lack of extensive population investigations in the last few years, designed like similar investigations from the sixties and seventies. Nevertheless, an indisputable fact is that these tumors are more common in settlements with BEN than in the other. This is primarily related with the UUC (16-18). These results are in absolute accordance with the UUC findings in other endemic regions on the Balkan penin-

sula (4-6). However, it is interesting that the settlements with BEN have a higher mortality of cancers localized out of the urinary tract (22) and the fact that the UUC is extraordinarily frequent in patients with analgesic nephropathy. Moreover, except frequency, many other clinical and epidemiologic characteristics of these tumors are similar in BEN and analgesic nephropathy (23,24).

This study demonstrated decreasing incidence of the UUC in the settlements where BEN is endemic during the whole period of study. These data are in agreement with the results of our previous reports. An investigation about the incidence of UUC in the settlements of the South Morava River basin during the 20-year period of 1969 to 1988 demonstrated 57 or 62 times greater incidence of these tumors in endemic than in non endemic villages and cities (18). The next investigation about the same problem in the 10 year period of 1989 to 1998 in the same region indicated that UUC was 11 times more frequent in endemic than in non endemic regions (25). This study demonstrates the increased trend for the UUC in non endemic villages and cities. This caused a very convincing increase trend, common for tumors of all examined settlements. Very similar results were obtained in the Jablanica region (26). This increased trend of the UUC, regardless of the kind of settlement is in accordance with the overall trend of the malignant diseases both in the world and our country.

This study demonstrated a trend towards less frequent occurrence of BEN, confirming our previous results (19). Similar results were obtained by Glogovac et al (27) investigating the incidence of BEN in Jablanica regions. Bukvic et al (28), however, point out persistent, relatively high incidence of BEN in Kolubara region. The author explains this attitude with a hypothesis that different endemic regions have specific local characteristics. The disagreement of different studies' results demands additional investigations. There is no new evidence about incidence of BEN and UUC in other endemic regions of former Yugoslavia, Romania and Bulgaria.

This investigation demonstrates a positive correlation between the trends of BEN and UUC in the endemic settlements. This observation gives rise to opinions that the etiopathogenesis of BEN and UUC is the same. These observations are supported by the facts that the age of patients with any of these diseases tends to increase although the finding is more convincing in the case of BEN. This finding points to slower progression of these disorders, which could be explained by decreased efficiency of the potential etiologic factors, or by weaker exposure, or less frequent contact with them, in their onset. Age structure shifting towards older age of BEN and UUC patients was documented by other authors (28,29). Before, BEN appeared most frequently in the third and fourth decades, and UUC in BEN regions in the sixth decade, according to them. Nevertheless, newer data show the most frequent appearance of BEN in the fifth and sixth decades, and UUC in the

seventh decade (28). Data like these are in considerable accordance with the data given in this work.

Significantly greater incidence of the UUC in the families with BEN than in the others was proven in this study. Otherwise, relatively frequent occurrence of the UUC in the families with BEN, was registered in the other BEN regions (8-10). However, families with BEN and UUC are characterized with higher risk of cancers outside the urinary tract (30). This significant positive correlation in BEN and UUC incidence trends and age structures, as well as family association of these disorders, suggests their common etiology. In previous studies, as a possible etiologic factors were indicated toxins

and viruses. Familial aggregation of these diseases gave rise to the hypothesis that genetic predisposition is one of the factors. However it is probable that these disorders occur in interaction of genetic and environmental factors. In any case, the tendency of decreasing the number of patients with BEN and UUC demonstrated in this investigation, indicates a very small efficiency of the potential etiologic factors in the occurrence of these diseases. Nevertheless, this requires further intensive observation of these factors, because the results of newer investigations in South Serbia show indisputable seasonal influence of environmental factors on renal function in children, especially in BEN regions (31).

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