BALKAN ENDEMIC NEPHROPATHY AND MALIGNANT UROTHELIAL TUMORS

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One of the features of Balcan endemic nephropathy (BEN) is higher frequency of urothelium malignant tumors, primarily of pyelon (Mtp) and urether (Mtu). Jablanica region is known for the presence of endemic, hypoendemic and non-endemic areas with BEN.

The aim of our research was to analyze the appearance of MTU in endemic settlements of Jablanica region with BEN and to see what the relation of tumor frequency between endemic and non-endemic settlements is.

The appearance of MTU was analyzed on the basis of operative protocol data of Urology department, The Health Center in Leskovac and Urology Clinic of The Clinical Center in Nis for the period from 1978 to 2002. We collected data about our patiens regarding their sex, age, the place of living and the place of birth. In order to make classification of settlements we used data of the Institute for Nephrology and hemodialysis (INH) in Nis. Data on total number of population living in these settlements were obtained from the official registration data published in 1981 and 1991. The incidence rate was calculated in the sample of 100,000 people.

The average annual incidence rate (AAIR) of MTU in endemic settlements for the considered period is 37.82 (tumors of urether and pyelon – 17.56; malignant tumors of urinary bladder (MTUB 20.26); in hypoendemic settlements the rate is 13.28 (MTp and Mtu – 5.06; MTUB – 8.22); and in non-endemic urban settlements it is 7.35 (Mtu and MTp – 1.04, MTUB – 6.31). AAIR of MTU in endemic areas is 2.85 times higher when compared to hypoendemic areas; it is 6.75 times higher than in non-endemic urban areas, and 5.15 times higher than the rate of non-endemic rural areas. Mtu and MTp are 18.68 times more frequent in endemic settlements than in non-endemic urban areas and 3.47 times more frequent when compared to hypoendemic settlements. The linear trend of the diseased from MTp and MTu in endemic areas of Jablanica region for 25-year period was slowly decreasing according to statistics ($y = -0.0054x + 0.59$; $r^2 = 0.0031$.

High frequency of Mtu, primarily of Mtu and MTp in areas with BEN, probably points to the common nephropathogenic and cancerogenic etiologic factor, confirming thus the existence of positive correlation between BEN and malignant tumors of upper urothelium (MTUU). *Acta Medica Medianae 2005; 44(1):15–20.*

Key words: *Balcan endemic nephropathy, malignant urothelial tumors, Jablanica region, type of settlements*

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Introduction

BEN is a chronic, familiar renal disease of slow progression mostly leading to destruction of renal parenchyma and the appearance of chronic renal insufficiency (1,2). It usually appears in plain regions of our country, Bulgary, Bosnia and Hercegovina, Bulgaria, Romania and Croatia (3). This disease was first described by Danilovic and associates in 1956 and 1957 and was noted in people living in Kolubara region (4).

One of the reasons of greater importance of BEN is its association with malignant tumors of urothelium (MTU), especially with malignant tumors of upper urothelium (MTUU), pyelon (MTp) and urether (Mtu). It is well-known that tumors of urothelium are more frequent in patients with BEN, their families as well as in patients living in risky areas (5,6,7,8,9,10).

Increased incidence of MTU after 1953 was registered not only in regions of former Yugoslavia, but also in other countries in the world. According to Petković, the frequency of MTUU in areas with marked BEN is 100 times higher than in control urban settlements, while frequency of renal tumors and tumors of urinary bladder did not show any significant differences (11). The same author also proved that MTUU appeared more frequently not only in patiens with BEN (10)% but also families. Radovanović and Krajinović confirmed Petkovic's findings and found significantly higher frequency of MTp and Mtu in endemic areas,

while MTMBs were equaly present in both regions. Analyzing 35-year-long presence of MTGU (1963–1998), Nikolić and associates (2002) found its higher frequency in endemic areas in comparison to pissibly endemic and non-endemic ones (13).

Many authors analyzed the connection between BEN and MTU in Bulgaria (Atanassov, 1974, Lambrev 1965). However, the authors from Romania could not find the association between these two diseases (Bruckner, 1965) (16).

Autopsies of patients died of BEN confirmed the existence of MTUB in 38% of cases (Petrinska and Lambrev). According to analyses of Bulgarian authors these tumors appeared in more than 30% of the diseased and according to Petkovic in 10% of BEN patients. Renal failure is more frequent in patients from BEN and endemic regions when compared to non-endemic regions (18).

Topografic distribution of MTU in the confluence of the River Juzna Morava has also been the subject of analysis in the last forty years. Strahinjic (1964) pointed to high frequency of these tumors in certain rural areas on the banks of the River Južna Morava (Brestovac, Pukovac, Nozrina etc.) which already had been known for BEN. Later, on the basis of operative findings of 20-year period and data obtained from INH in Nis, Kovacevic (1970) made the chart of topografic distribution of these two diseases. These findings were further analyzed and proved by Cukuranovic and associates (1987, 1991, 2002) and Markovic. (2001). Many authors found higher frequency of MTUB in endemic areas (Cukuranovic and associates, 1987, 1991; Stefanovic and Polenakovic, 1991; Markovic, 2001; Glogovac, 2002) in comparison to non-endemic ones with BEN.

Regarding renal disease, Jablanica region is inappropriate in epidemiological sense, primarily for the existence of endemic areas with BEN and higher frequency of MTU. Stojanovic and associates (1987) first pointed to high frequency of MTUU both in endemic areas and non-endemic village Rudare (1987) (26). Analyzing MTUU in Jablanica region, Glogovac and associates (2001) pointed to higher frequency of MTUU in endemic areas, but also in certain non-endemic settlements (Brejanovac and Rudare) (27, 28, 29, 30).

Material and methods

The analyzed period lasted from 1th of January 1978 to 31th of December 2002. During analysis of MTU frequency, we used the operative material of Urology department of the Health Center in Leskovac and Urology Clinic of Clinical Center in Nis. Patients were devided according to the place of living within certain areas. To make classification of these areas, data of INH CC Nis were used (A-endemic areas, B-hypoendemic, C-non – endemic urban D–non-endemic rural areas). Facts on total number of Jablanica region population were collected accoding to official registration data from 1981 and 1991. The incidence rate was calculated in the sample of 100,000 persons. Only for practical reasons, we joined groups C and D (non-endemic areas) during the observation of MTUU and MTUB. Statistic significance is on the level of p<0,05.

Results

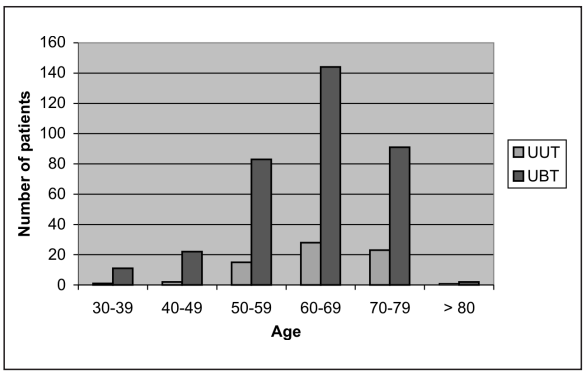
During the period from 1987 to 2002, 467 cases of malignant tumors of urothelium were registered in Jablanica region: 83 MTUU and 384 MTUB. From 467 registered tumors, 344 (73,66%) appeared in males and 123 (26,34%) appeared in females. (Table 1, 2; Graph 1, 2, 3, 4).

Table 1. Distribution of MTUU in Jablanica region from 1978 to 2002 regarding tumor type and place of living

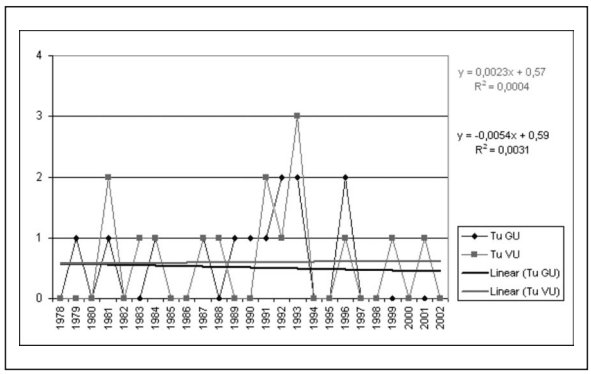
Group	UUT		UBT		UUT and UBT AARI	p
	Numbers of patients	Average Annual Rate of Incidence	Numbers of patients	Average Annual Rate of Incidence		
A	13	17.56	15	20.26	37.82	p>0.05
B	8	5.06	13	8.22	13.28	P<0.05
C	18	0.94	89	4.66	5.60	P<0.01
D	44	1.04	267	6.31	7.35	P<0.01
Total Area	83	1.30	384	6.02	7.32	P<0.01

Table 2. Distribution of AAIR MTU in Jablanica region from 1978 to 2002 regarding gender and age

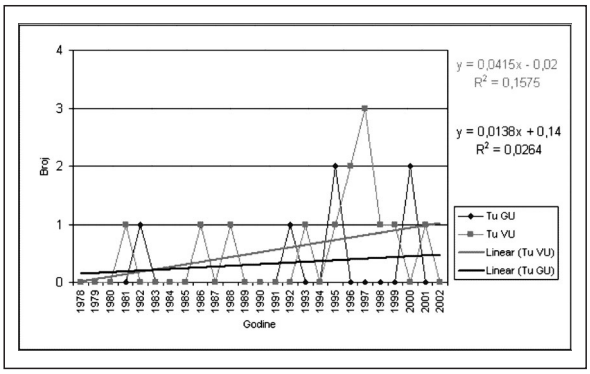
Year	30-39		40-49		50-59		60-69		70-79		80+		Total	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Endemic	-	-	-	-	2	1	2	2	3	3	-	-	7	6
Hypoendemic	-	1	-	-	1	-	-	3	2	1	-	-	3	5
Nonendemic	1	-	2	-	8	4	11	14	8	13	-	1	30	32
Total	1	1	2	-	11	5	13	19	13	17	-	1	40	43



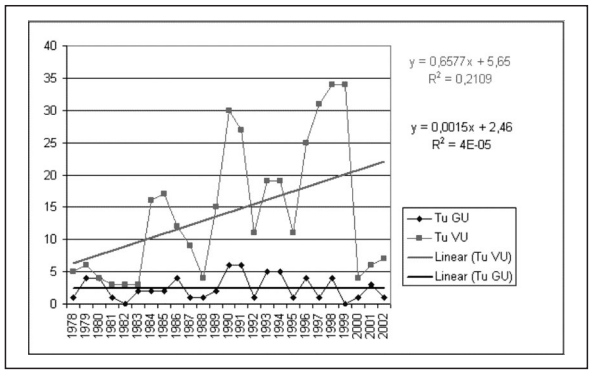
Graphic 1. Distribution of MTU in Jablanica region from 1978 to 2002 regarding age



Graphic 2. The linear trend of the diseased from MTU in Jablanica region from 1978 to 2002 in endemic settlements



Graphic 3. The linear trend of the diseased from MTU in Jablanica region from 1978 to 2002 in hypoendemic settlements



Graphic 4. The linear trend of the diseased from MTU in Jablanica region from 1978 to 2002 in non-endemic settlements

Endemic, non-endemic and hypoendemic areas with BEN are situated in Jablanica region. The incidence of the diseased from MTU is shown in Table 3.

Discussion

From the point of view of renal disease, Jablanica region is inappropriate in epidemiological sense, primarily for the existence of endemic areas with BEN and higher frequency of MTU. In his collective serial about BEN, Petkovic found that frequency of MTUU in endemic areas is 20-100 times higher than in non-endemic ones. Stojanovic and associates (1987) were first to point to high frequency of MTUU both in endemic and certain non-endemic settlements of Jablanica region (Rudare). These results demand further reseach of certain non-endemic areas, especially for the fact that the number of patients on hemodialyses is greater in these settlements (Glogovac 2001, 2002).

AAIR MTU was 37,82 in period from 1978 to 2002 in endemic settlements of Jablanica region. The rate is considerably lower in hypoendemic (13,28) and non-endemic urban settlements (5,60) and in non-endemic rural settlements (7,35). These facts point to the conclusion that people in endemic settlements have MTU 2,85 times more frequently in relation to hypoendemic ones; 6,75 more frequently in relation to non-endemic urban and 5,15 in relation to non-endemic rural settlements. Regarding the same period, MTUU is 3,47 times more frequent in endemic settlements in relation to hypoendemic ones; 18,68 times more frequent in relation to non-endemic urban settlements and 16,88 times in relation to non-endemic rural settlements. At the same time, in hypoendemic settlements, MTUU are 4,87 times more frequent in non-endemic rural settlements and 5,38 times more frequent in relation to non-endemic urban settlements. Obtained results are different from Cukuranovic and

Table 3. Distribution of MUBT of Jablanica region from 1978 to 2002 in relation to gender and age

Year	30-39		40-49		50-59		60-69		70-79		80+		Total	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Endemic			1	1	3		5	1	4				13	2
Hhypo-endemic					2	1	8		2				12	1
Nonendemic	8	4	19	4	65	19	115	24	72	24		2	279	77
Total	8	4	20	5	70	20	128	25	78	24		2	304	80

associates' results (1987) pointing out that MTUU are 57 times more frequent in endemic settlements of the River Juzna Morava confluence when compared to non-endemic settlements, 62 times more frequent in relation to surrounding urban non-endemic settlements. Markovic (2001) found that MTUU in endemic settlements of the Juzna Morava confluence in the period from 1989 to 1998 were 11,2 times more frequent than in surrounding non-endemic settlements. At the same time, he found that the incidence of these tumors in hypoendemic settlements was 6 times higher than in non-endemic settlements.

Regarding the incidence of MTUB, our research points to the highest AAIR incidence in patiens from endemic areas (20,26), while in hypoendemic (8,22) and non-endemic it is significantly lower (4,66 and 6,31). The facts say that people in endemic settlements have MTUB 2,46 times more often in relation to hypoendemic settlements; 4,38 times more frequent in relation to surrounding non-endemic urban settlements and 3,20 times more frerquently in relation to surrounding non-endemic rural settlements.

The age and sex structure of patients with MTU in Jablanica region show that males 40,99% (141/344) and females 19,51% (24/123) get this disease at the age of 60 to 69.

The incidence of UT regarding sex showed insignificant differences of MTUU (males 40 vs females 43) and very significant differences of UBT (males 306 vs females 78). Considering the urinary bladder tumor presence , this search pointed to the highest annual rate of incidence in case of patients coming from endemic settlements (20,26). It is significantly less (8,22 and 5,79) in case of hypoendemic and non-endemic settlements. Comparing MTUU and MTUB we noted insignificant differences within A group (17,56 vs 20,26) ($p>0,05$), and very significant difference within D group (1,04 vs 6,31) ($p<0,01$). But, in some places in D group the incidence of MTUU was very high -as in Brejanovac (AAIR is 40,50).

Regarding MTUU, females almost have the same incidence as males (1:1,075), while the situation is complitely different with MTUB where males have it 3,8 times more frequently than females: in endemic settlements (6,5:1), in hypoendemic (12:1) and non-endemic ones (3,62:1).

The linear trend of MTUB diseased of MTUU diseased in endemic settlements of Jablanica region during 25-year period was slowly dicreaseing according to statistics ($y=-0,0054x + 0,59$; $r2 =0,0031$) which coincides with the results of Marković's 10-year-long study. The linear trend of MTUB diseased in Jablanica region in the considered period was satistically increasing only in non-endemic settlements ($y= 0,6577x + 5,66$; $r2=0,2109$).

The results of 25-year-long research show that MTUU appear in Jablanica region in 25,30% (21/83) in endemic and hypoendemic settlements, while in non-endemic settlements it is presented with 74,70% (62,83). The results are significantly different in relation to the research done in the surrounding of Lazarevac, where patients with MTUU coming from endemic settlements (Bukvic 1996, 1999) are present in high percentage (89,04%). Relatively low percentage of MTUU in Jablanica region in endemic settlements in relation to Lazarevac is explained by surprisingly high incidence in certain rural non-endemic settlements.

Conclusion

High frequency of urothelium malignant tumors, primarily malignant tumors of urether and pyelon in the regions with Balkan endemic nephropathy incidence, probably points to the common nephropathogenic and cancerogenic etiologic factor and proves the existence of positive correlation between BEN and malignant tumors of upper urothelium.

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BALKANSKA ENDEMSKA NEFROPATIJA I MALIGNI UROTELIJALNI TUMORI

Stevan Glogovac, Vidojko Đorđević, Jasmina Tomin, Jelena Živanov-Čurlis, Svetislav Kostić, Nebojša Prokopović i Dragoslav Bašić

Jedna od karakteristika Balkanske endemske nefropatije(BEN) je veća pojava malignih tumora urotelijuma(MTU), u prvom redu malignih tumora pijelona(MTp) i uretera(MTu). U Jablaničkom okrugu nalaze se oblasti koje su endemske, hipoendemske i neendemske za BEN.

Cilj rada je bio ispitivanje pojave MTU u endemskim naseljima Jablaničkog okruga za BEN i odnosa učestalosti tumora u endemskim i vanendemskim naseljima.

Pojava MTU analizirana je na osnovu podataka operativnih protokola Urološkog odeljenja Zdravstvenog centra Leskovac, Urološke klinike Kliničkog centra Niš za period od 1978. do 2002. godine. Za sve bolesnike sakupljeni su podaci o polu, starosti, mestu stanovanja i rođenju. Za klasifikaciju naselja, korišćeni su podaci Instituta za nefrologiju i hemodijalizu (INH) Niš. Podaci o ukupnom broju stanovnika u naseljima dobijeni su na osnovu zvaničnih podataka obavljenog popisa stanovništva 1981. i 1991. godine. Stopa incidencije je računata na 100 000 stanovnika.

Prosečna godišnja stopa incidencije(PGSI) MTU u endemskim naseljima za posmatrani period je 37.82 (za tumore uretera i pijelona 17.56; tumore mokraćne bešike/MTMB/ 20.26) u hipoendemskim 13.28 (za MTp i MTu 5.06; MTMB 8.22) u neendemskim gradskim naseljima 5.60(za MTu i MTp 0.94; MTMB 4.66) i u neendemskim seoskim naseljima 7.35(za MTu i MTp 1.04; MTMB 6.31).

PGSI MTU u endemskim naseljima veća je 2.85 puta od stope u hipoendemskim, 6.75 puta veća u odnosu na stopu u neendemskim gradskim naseljima a 5.15 puta veća u odnosu na stopu u neendemskim seoskim naseljima. MTu i MTp češći su u endemskim naseljima 18.68 puta nego u neendemskim gradskim naseljima, 16.88 puta češći u odnosu na neendemska seoska a 3.47 puta češći u odnosu na hipoendemska naselja. Linearni trend obolelih od MTp i MTu u endemskim naseljima Jablaničkog okruga za 25-godišnji period bio je u statistički slabom opadanju ($y=- 0.0054x+0.59$; $r^2=0.0031$).

Visoka učestalost MTU, a u prvom redu MTu i MTp u regionima sa BEN, možda ukazuje na zajednički nefropatogeni i kancerogeni etiološki faktor i potvrđuje postojanje pozitivne korelacije između BEN i malignih tumora gornjeg urotelijuma. *Acta Medica Medianae 2005;44(1):15–20.*

Ključne reči: *Balkanska endemska nefropatija, maligni urotelijalni tumori, Jablanički okrug, tip naselja*