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MALIGNANT BLADDER TUMORS AND BALKAN ENDEMIC NEPHROPATHY: POSSIBLE COMMON ETIOLOGIC FACTORS

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Summary. *The aim of this work is to establish the most important epidemiologic features of malignant bladder tumors (based on the investigations so far), to get an insight into the risk factors and explain possible association with Balkan endemic nephropathy. Data from the most important studies were used, published in the country and abroad in scientific literature. Morbidity and mortality rates were expressed per 100.000 inhabitants. The most common primary malignant bladder tumors are: carcinoma transitocellulare (80-90%), planocellular carcinoma (3-7%), adenocarecinomas (1-2%) and malignant sarcomas (1%). Bladder cancer belongs to the group of 12 most frequently registered new malignant tumors per year, in both sexes, and in industrial countries it is even more common. People living in highly developed countries in Europe and North America are most frequently affected, as well as those in the regions with endemic schistosomiasis (Africa) and Taiwan. In highly developed countries bladder cancer mortality demonstrates the lowest degree of variability compared to other regions. Mortality rates are higher in male population. Bladder cancer affects mainly male population. Male/female ratio differs from country to country and it is usually 4:1, but there are regions with much higher or lower ratio. The highest incidence and mortality rates are registered in those over 75 years of age (more than 140/100.000 men) or those over 30 in female population. The connection of bladder cancer to upper part urothelial tumors has been established in many investigations, but this connection for bladder cancer was seen only in some recent studies. According to different investigations, the incidence of bladder malignant tumors was 1.5 to 8.4 (mainly 3 to 4) times higher in the endemic regions for BEN versus the non-endemic. Possible common etiologic factors for BEN and malignant bladder tumors, established in various independent studies may be: genetic basis, lack of oligoelements and antioxidants in food and drinking water, and exposure to different aromatic hydrocarbons. Both BEN and urothelial tumors (bladder cancer as well) are probably the diseases with multifactorial etiology, for the occurrence of which, in addition to genetic hypotheses, environmental factors are responsible too. It may well be spoken of the same external factors the effect of which depends on their concentration in an organism, duration of exposure and type of cells they act upon. However, to establish the etiology of both diseases it is necessary to perform many multidisciplinary studies including scientists from various fields: geneticists, toxicologists, clinical physicians, epidemiologists, geologists and others.*

Key words: *Bladder cancer, Balkan endemic nephropathy, etiology*

Introduction

Twenty or more years ago, the pioneer in endemic nephropathy studies, the Academy member Sava Petković, suppposed that the whole urothelium, bathed in urin, is permanently exposed to various harmful agents, even cancerogenic substances (1), ingested or produced as metabolic by-products. It is no wonder, thus, that the whole urotract, including the bladder, is one of the most frequently affected systems in the organism by various malignant and benign neoplasms. However, in spite of all the efforts, the etiology of the disease has not yet been fully elucidated.

The aim of this work is to establish the most important epidemiologic features of malignant bladder tumors (based on the investigations so far), to get an insight into the risk factors and explain possible association with Balkan endemic nephropathy. Data from the most important studies were used, published in the country and abroad in scientific literature. Morbidity and mortality rates were expressed per 100.000 inhabitants.

Histopathologic characteristics of bladder tumors

The bladder may be affected by benign, malignant primary and malignant secondary tumors. Benign bladder tumors most frequently originate from the transitional epithelium and they are usually called papillomas.They are most frequently encountered in the trigone region and after surgical removal they tend to recur. Due to their propensity to transform into malignancies, they are categorized as pre-cancerous lesions (2); their

development into carcinoma occurs in several phases, from atypia, through carcinoma in situ, to invasive carcinoma. In addition to papillomas, benign tumors of mesodermal origin (fibromas, fibromyxomas, myxomas, leiomyomas, neurofibromas, xantomas, angiomas, granulated-cell myoblastomas, dermoides and osteomas) are also found in the bladder (3).

The most common primary malignant bladder tumor is carcinoma transitonal cell. It originates from the transitional epithelium; 80-90% of all bladder malignancies are of this type. By the degree of cell differentation we recognize 4 types, with the I degree as the least malignant and IV degree as the most malignant. In approximately 25% of these tumors, plaques of tubular cells are found, increasing malignant potentials of the tumor.

The next most frequent bladder tumor is planocellular carcinoma (3-7%), somewhat more benign than the previously mentioned one; in 1-2% adenocarcinomas occur originating from the periprostatic, periurethral glands or urachus.

Malignant sarcomas, though extremely rare (1%) may also affect the bladder.

The most frequent secondary malignancies affecting the bladder are those that spread from the adjecent organs (direct invasion - cervix, uterus, prostate, rectum), those implanted from primary tumors of the upper urotract regions, or distant metastases (lung, stomach, breast). Lately, reports demonstrate primary malignant bladder tumors occuring simultaneously with malignant prostate tumors (5), testicular tumors (6) or renal malignancies (7). Malignant bladder tumors are most frequently found on its side walls (37.1%), posterior wall (17,9%), trigone (12.6%), neck (11.1%), ureteral orifice region (9,8%), and anterior wall (3.8%). Tumors in the upper parts and anterior wall are usually found in older individuals (75 and over) and tumors in the trigone and ureteral orifice regions accur usually in those below 70 years of age (8).

Incidence and mortality

Bladder cancer belongs to the group of 12 most frequently registered new malignant tumors per year (9), in both sexes, and in industrial countries it is even more common. People living in highly developed countries in Europe and North America are most frequently affected, as well as those in the regions with endemic schistosomiasis (Africa) and Taiwan. Over 170.000 people worldwide are affected by bladder cancer. During the 1970s, standardized bladder cancer incidence rates were for men from 0.9 (New Zealand) to 21.0 (England and Wales) and for women from 0.2 (Israel, non-Jewish population) to 5.9 (USA) per 100.000 inhabitants (10). Matanoski (11) states that the highest incidence was observed in Africa (Bulawago): 28.7 for men and 7.0 for women, and the lowest incidence in India (2.9 for men and 1.1 for women). High incidence rates were also observed in Taiwan and regions endemic for "black foot disease": 23.5 for men and 21.1 for women, while in other regions of Taiwan those rates are low (12). Many studies demonstrate the increasing incidence trends of bladder cancer in male population, while in female population incidence slightly decreases (13,14).

In highly developed countries bladder cancer mortality demonstrates the lowest degree of variability compared to other regions. Mortality rates are higher in male population. Standardized mortality rates during the 1960s were from 2 to 8 for men, and from 1 to 2.5 for women per 100.000 (11). At the end of the 1980s, bladder cancer mortality rates were 2.1-9.0 (men) and 0.1-2.2 (women) (15).

Age and sex

Malignant bladder cancer affects mainly male population. Male/female ratio differs from country to country and it is usually 4:1, but there are regions with higher (30:1 in Israel in non-Jewish population) or lower ratio (1:1.9 in Taiwan -regions with endemic "black foot disease"); in some regions of the world bladder cancer incidence is even higher in female popuilation (New Zealand, Maoris - 0.3:1) (12,16).

Simmilar relations were observed among those who died from bladder cancer.

Highest incidence and mortality rates are registerd in those over 75 years of age (more than 140/100.000), or those over 30 in female population. In younger age groups incidence and mortality rates are lower; bladder cancer is rarely detected in those below 30 years of age.

Survival

Stephenson (8) points out that 1-year survival is 87%, 2-year survival 74% and 5-year survival 54%, and that survival depends on the anatomic site of the tumor, age of the patient and exposure to chemical cancerogens: professional bladder cancer is associated with worse prognosis and shorter survival.

Hypothesis on bladder cancer risk factors

The earliest works on bladder cancer etiology can be traced back to the end of the 19^{th} and beginning of the 20^{th} century, when some risk factors were discovered - some paints and parasitic infections (Schistosoma hematobium) (17). Up to the present, many investigations have been performed, establishing other bladder cancer risk factors: exposure to various chemical cancerogens (most significant were aromatic organic compounds and halogenous derivatives of aromatic carbohydrates - naphtylamines, benzidines, aniline) (18), tobacco smoking (19,20), coffee and alchocol consumption (21,22), artificial sweeteners usage (23), lack of vitamine A, beta-carotene, alpha-tocopherol, selenium, lykopen and the other antioxidant substanties in food (14,25,26), long-lasting use of phenacetin based drugs (27), cyclophosphamide (28), isoniasid (29), as well as

previous renal and bladder diseases (urolithiasis, cystitis, urethral infections) (30,31). Use of drinking water contaminated with trichlorethylene, tetrachlorethylene and other solvents (32), as well as use of chlorinated water (33) are also bladder cancer risk factors; it is also demonstrated that these tumors tend to occur more frequently in the families with more frequent occurence of malignant tumors in general, suggesting possible genetic predisposition (34,35,36).

Bladder tumors and Balkan endemic nephropathy

During the 1950s, it vas observed that tumors of the urogenital tract, especially renal pelvis and ureteral ones, are much more common in the communities with BEN. Professor Danilovic (quotation by S. Petković - 1) observed back in 1957 this unusual phenomenon and reported that in 560 persons with endemic nephropathy some tumors were simulataneously detected in 55 cases, mostly in the pelvis and urether. Several years after that (1963,1964), Bulgarian scientists reported that in autopsy of endemic nephropathy cases malignant tumors of the urotract are found in 37.7%, among which a significant percent of bladder malignancies (37).

At the Congress of Italian Urologic Association in 1965, S. Petković et al. reported their findings:120 cases of renal pelvis and 60 cases of uretheral tumors assocoated with BEN (1). However, the findings of our and Bulgarian experts on the bladder cancer incidence in the regions endemic for BEN do not match. While Bulgarian results suggest increased incidence of these tumors too, our studies from the beginning of the 1970s demonstrate even lower incidence in the endemic regions compared to general population. Geographical distribution of 1625 cases of bladder cancer registered by the Clinic of Urology in Belgrade during the 1950s and 1960s matched geographical distribution of large industrial centres, without correlation with geografical distribution of BEN. This disagreement of our and Bulgarian scientists was explained as different methodologies of work: Bulgarian findings were based on autopsy findings and our findings on clinical material (1).

More frequent bladder tumor occurence in the regions endemic for BEN was first observed by Žikić on the material of the Clinic of Urology in Niš (quotation by Petković -1). He reported that bladder tumors are 2.5 times more frequent in endemic compared to other regions, but these data were not commented by Petković.

At the Symposium on Balkan Nephropathy held in Niš in 1983, 5 papers were reported on urinary tract tumors in BEN; none of them demonstrated increased incidence of malignant bladder tumors in endemic regions, though Bulgarian authors (38) reported that in 112 patients with BEN and malignant tumors, in 16 cases they observed malignant bladder tumors.

At the beginning of 1990s, an investigation was performed in Serbia (hyperendemic village Petka, Belgrade county) demonstrating, however, that bladder cancers are not more common in the regions with BEN. The investigation was based on the mortality data in the cohort of 416 persons aged 4 and over, monitored for 15 years (1974-1988) (39).

However, at the end of the 1980s and beginning of the 1990s on the material from 474 patients with tumors of the urinary tract at the Clinic of Urology in Niš (1971-1986), Dept. of Urology in Leskovac (1975-1986) and Institute for Haemodialysis in Niš (1968-1986), Čukuranović et al. (40,41) demonstrated that the geographical distribution of these tumors matched that of BEN; that the urinary tract tumor incidence trends were going upwords (especially for bladder tumors); that tumors of the upper urothelium were most common in the 6^{th}, while bladder tumors were most common in the 7^{th} decade of life; that bladder tumors were 1.7 more frequent in endemic regions compared to hypoendemic ones, and 3.2 times more frequent than in non-endemic regions; in endemic regions renal pelvis and ureteral tumors comprise 64.5% and bladder tumors 35.5% of the cases, but in hypoendemic, non-endemic and urban regions bladder tumors are more frequent than upper part urothelium tumors (42). However, in the papers quoted, authors did not pay special attention to malignant bladder tumors but predominantly to upper part urothelial tumors. In the next investigation performed in the same region, enrolling 659 examinees inhabiting the basin of the South Morava river (1969-1988), the authors paid special attention to bladder tumors, demonstrating the average annual incidence rate in endemic regions of 19.5, in hypoendemic 7.8 and only 1.6 in rural and 2.3 in urban non-endemic regions. Bladder tumors were 7 times more frequent among families with BEN compared to the families without BEN (43). Similar observations were reported by Stefanović in 1998 (44).

Petrović in his works from 1996 and 2001 paid special attention to bladder tumors and BEN, reporting the folloving results: In the former Niš region with only one registered case of BEN since 1986, 258 malignant bladder cancers were reported and in the rest of the region 114. Having in mind the number of inhabitants, relative risk for bladder cancer in the settlements with BEN is 1.5 (CI 95% = 1.14-1.99) and chi-square test demonstrates high statistical significance ($\chi^2 = 26.28$, $p = 0.0000$). In endemic regions for BEN, cummulative incidence rate for bladder cancer (222.7) is 3.8 times higher compared to non-endemic regions (58.0) (45,46).

In his investigation Marković (47) stated that malignant bladder cancer was 2.3 times more common in endemic than in non-endemic regions of the South Morava basin in the period from 1989 to 1998. Average annual incidence rate of malignant bladder tumors in endemic regions of the South Morava basin was 35.70 and 15.35 in non-endemic. In the same period, bladder cancer trends in endemic regions were going downwords (y=58.344-2.629x), while in non-endemic an upward tendency was registered (z=12.372+ 0.271x). According to erlier investigations by Čukuranović et al.

endemic nephropathy tendencies in the region were decreasing (48,49).

In almost all new investigations of the general population it has been established that malignant tumors of the bladder were 3-4 times more frequent in men, and the highest age-specific rates were registerd in the age group 70-74. However, according to Marković, male to female ratio in endemic regions was 2.7:1 and in non - endemic 5.7:1 (47). According to earlier studies, maximal incidence rates for BEN were observed for the age group 50-55, and both sexes are equally affected (women even slightly more).

Based on the investigations so far, the most important etiologic factors and/or risk factors for BEN and bladder cancer are given in the table 1.

Table 1. Risk factors for BEN and bladder cancer

Risk factors	Bladder cancer	BEN
Schistosoma haematobium	+	
Smoking	+	
Artificial sweeteners	+	
Coffee	+	
Bladder inflammation	+	
Phenacetin	+	
Aromatic hydrocarbons	+	+
Genetics	+	+
Selenium deficiency	+	+
Heavy metals (Pb, Cd, Cr)		+
Viruses		+
Mycotoxins		+

In the light of these facts, there is no doubt that BEN is somehow associated with malignant bladder tumors. However, the nature of the association and/or common etiology still need to be established. The available facts suggest the possibility of common etiologic factors, but with different mechanisms of action: for BEN, etiologic factors act as toxic agents producing consequences fast, while for malignant tumors these factors are cancerogenic requiring a longer period of time to express their action.

Possible common etiologic factors for BEN and malignant bladder tumors, established in various independent studies, may be: genetic determination, lack of oligoelements and antioxidants in food and drinking water, and exposure to different aromatic hydrocarbons.

Genetic factors, no doubt, may be of significant influence either directly (genetically determined diseases) or indirectly, influencing the quality of tissues and organs, immune response, various metabolic, detoxication and excretory protective processes. Both for BEN and bladder cancer the question is not in hereditary diseases in the narrow sense of the word, but in genetically determined responses to the presence of harmful agents, enabling them to exert their toxicity and/or cancerogenic features in a greater degree. For instance, in individuals with cancer of the bladder, reduced detoxication (acetylation) rate was observed; this process determines the presence of cancerogens in the urin (50,51).

Smokers, who are simultaneously "slow acetylation phenotypes", have larger quantities of hemoglobin-4-aminobiphenyl (a cancerogen) in the urine, which is a metabolite of aromatic amines contained in the cigarette smoke. In the autopsy material of the bladder, there is more DNA-adducts made of 4-aminobiphenyl in smokers. The differences were registered in BEN too, in the activity of enzymes involved in detoxication. The differences among various individuals in gene variations coding cytochromes P450, such as CYP1A1, CYP2D6, CYP2E1 and polymorphism in glutathione-S-transferase and N-acetyl-transferase 1 and 2 (52,53). Besides, the sensitivity to antioxidants and other substances with protective role in disease etiology is also genetically determined.

Lack of selenium, in BEN etiology (54) as well as bladder cancer (25), was established in several investigations. However, lack of selenium may cause other diseases as well (for example, endemic cardiomyopathy in China). The latest investigations suggest that vitamin C, vitamin A, beta-caroten, alphatocopherol, selenium, lykopen and other antioxidants lessen the possibility of free radicals production, and selenium is directly involved in immune antitumotal response. From this point of view, selenium defficiency may provoke many diseases, malignant ones included, so it is not specifically responsible for BEN and malignant tumors of the urotract.

The most interesting hypothesis about the common etiology of BEN and malignant urothelial tumors (bladder cancer included) is the one implicating various aromatic (less aliphatic) hydrocarbons. There is a spectre of various hydrocarbons with nephrotoxic and/or cancerogenous action, entering the organism in various ways and provoking diseases. It was first established that occupational exposure to naphthylamines, benzidine, aniline, o-toluidine, but crude oil, coal tar, machine oil as well, has a very important role in bladder cancer aetiology. Investigations several years ago demonstrated that in endemic regions there are several times more PAHs in the drinking water compared with non-endemic regions (55). One of the theories was that they originated from the lignite surface mines (56). However, to confirm the theory, it is necessary to answer the following questions: why in some regions with pliocene lignite there is no BEN and are in these areas urothelial tumors more common (including bladder cancer) (57,58). Whether the toxicity and/or cancerogenic features of polyaromatic hydrocarbons (PAHs) are equally harmful to upper part urothelium and bladder urothelium, and why bladder cancers occur less frequently than upper part urothelial tumors? Does the concentartion of PAH in drinking water correlate with the amount of BEN and urothelial malignancies? In view of the fact that in areas with established higher PAH concentration BEN incidence is decreasing, does this reflect PAH concentration fall?

In any case, both BEN and malignant urothelial tumors (bladder cancer as well) are probably the diseases with multifactorial etiology, for the occurence of which,

in addition to genetic factors, environmental factors are responsible too. It may well be spoken of the same external factors the effect of which depends on their concentration in an organism, duration of exposure and type of cells they act upon.

To establish the etiologies of both diseases it is necessary to perform many multidisciplinary studies including scientists from various fields: geneticists, toxicologists, clinical physicians, epidemiologists, geologists and others.

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