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# PROCEEDINGS

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## XXIII International Conference Ecological Truth

**Editors**

**Radoje V. Pantovic**

**Zoran S. Marković**

*EcoIst '15*

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**Hotel "PUTNIK", Kopaonik, SERBIA  
17-20 June 2015**

UNIVERSITY OF BELGRADE  
TECHNICAL FACULTY BOR



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"ECOLOGICAL TRUTH"**

*Eco-Ist'15*

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**THE MEDICAL-GEOGRAPHICAL ASPECTS OF ENDEMIC  
NEPHROPATHY IN THE MUNICIPALITY OF LAZAREVAC**

**Stefan Denda<sup>\*</sup>, J. Stojanovic**

University of Belgrade, Faculty of Geography, Belgrade, SERBIA

*\*stefandenda1990@yahoo.com*

**ABSTRACT**

Endemic nephropathy is a chronic non-communicable disease related to the Balkans. Therefore, the aim of the paper is to emphasise the notion of endemic nephritis with special reference to the municipality of Lazarevac by the use of medical-geographical methods. Conditionally, the paper can be divided into five segments: the first, related to the concept and causes of the disease, the second, to the specifics of the municipality of Lazarevac in relation to nephritis, the third, to the results of clinical studies of endemic nephropathy, the fourth, to the function of the special hospital, and the conclusion, which sublimates previous findings.

**Key words:** endemic nephropathy, Lazarevac, focal points, factors, treatment.

**INTRODUCTION**

The Balkan endemic nephropathy (BEN) is a hereditary, tubulointerstitial and chronic kidney disease unique only to limited parts of the rural population of Southeast Europe. It is a non-inflammatory disease which eventually leads to the deterioration of kidney tissue and its gradual function failure in terms of chronic renal insufficiency (weakness). Bearing the prefix "Balkan" in mind, the conclusion is that it occurs in Serbia, but it also occurs in the territory of Bosnia and Herzegovina (Semberija, Bosanski Šamac, Brčko and Modriča), as well as Croatia (Slavonski Brod and Županja). Apart from the countries of former Yugoslavia, the focal points have been detected in 44 settlements in the Republic of Bulgaria (areas of Vraca and Mihajlovgrad), as well as in 41 settlements in the Republic of Romania [1]. As one of the major geographic disciplines, medical geography, using numerous methods, deals with the study of various communicable and non-communicable diseases, and therefore endemic as a particular and specific segment of the population morbidity. It sublimates all data obtained from the field or clinical studies in the form of cartographic and statistical models, as well as in the form of a spreadsheet of medical and demographic statistics [2]. Bearing in mind the fact that this is a problem which is "domesticating" in specific population and spatial framework, nozogeography approaches its study very thoroughly. Based on this, the Municipality of Lazarevac is a focal point of endemic nephropathy on the territory of Serbia [3].



## **ETIOLOGY OF ENDEMIC NEPHROPATHY**

Endemic nephropathy, also known as “the mystery of the Balkan kidney”, still has an unknown etiology. Despite the fact that there has been more than a few decades of various research in this part of Europe, the results are not particularly favourable, since they are based on assumptions. As it is the case with these diseases and all others, most authors take genetic factors as a general guideline for endemic nephropathy. It may have been the first assumption of the science of the old 1960s when it was named “a hereditary and chronic disease.” But the claim that this is a hereditary disease has not been proved, thus forcing the conclusion that the factors of heredity do not play a key role in its exposure. For this reason, a completely different thesis has been considered, according to which the disease occurs due to numerous animate and inanimate environmental factors. Systematic research led to the relevant proof that protozoa, bacteria and rickettsia do not affect the occurrence of the Balkan nephritis. Little is known about the importance of viruses as another biotic agent in addition to bacteria and fungi, but there used to be unconfirmed claims that the “West Nile Virus”, which is transmitted by birds, could be associated with endemic nephropathy. Another possible stronghold cited was also the impact of “Ochratoxin A” (OTA), a product of fungi which pollutes cattle food, and is indirectly found in human blood and tissues, which is why it is thought to be responsible for nephropathy and closely associated urinary tract tumors [4]. The research went in different directions, which is testified by the thesis that the occurrence of the Balkan nephritis is due to numerous agents of the inanimate environment, especially lead as an extremely carcinogenic element which could be found in water, mill stones and flour for human consumption. Special attention was also paid to cadmium, which is up to ten times more toxic than arsenic, causes kidney and muscle damage, and has an emphasized carcinogenic effect as well. Unfortunately, none of these hypotheses have been scientifically justified or confirmed. Bearing in mind the prior knowledge that endemic nephropathy occurs exclusively in rural areas of river basins, major efforts have been directed to assess the hydrogeological environmental factors and their impact on the incidence of the disease. In terms of hydrogeology, endemic settlements are more often found on alluvial sediments which cover the old tertiary sediments, and less often on river and lake terraces which rise above the river plains. The approach was taken in this direction to thorough checks of physical and chemical composition of host rocks where drinking water was found. It was concluded that it was mostly areas below 200 m, and further efforts were directed at the analysis of household well waters. The analysis covered their temperature, Ph value, the content of silicon dioxide, nitrates, numerous chemical elements and ions, yet unfortunately it did not lead to any particular crucial evidence. Evidence has shown, however, that during the course of summer the well waters mix with the contaminated underground waters in villages that use them, when the well waters are at a very low level, which consequently makes such households the focal points of endemic nephropathy. If we consider that the municipality of Lazarevac and Lajkovac are among the most vulnerable areas, the connection between surface coal mining and the incidence of the disease has been sought for a longer period of time. The effort was made to determine the effect of lignite and its impact in terms of coal deposits and by-products resulting from washing the coal before

dry separation [5]. This is the way the aromatic hydrocarbons and amines soluble in water were created, whose effects are highly malignant and therefore considered responsible for the higher incidence of urothelial cancer. Many oligoelements whose lack or excess could cause this disease were also taken into consideration. Special attention was focused on selenium which is known for its anti-cancer effect, strengthening of the immune system and resistance, and the fact that its deficiency leads to the inability of cells to defend themselves against the impact of toxic substances and organic carcinogens from the environment. When it comes to endemic areas, zinc deficiency was discovered alongside selenium (outstanding defensive element, important for the immune system), but on the other hand, high concentrations of iron and magnesium (up to 13 times higher than in non-endemic settlements).

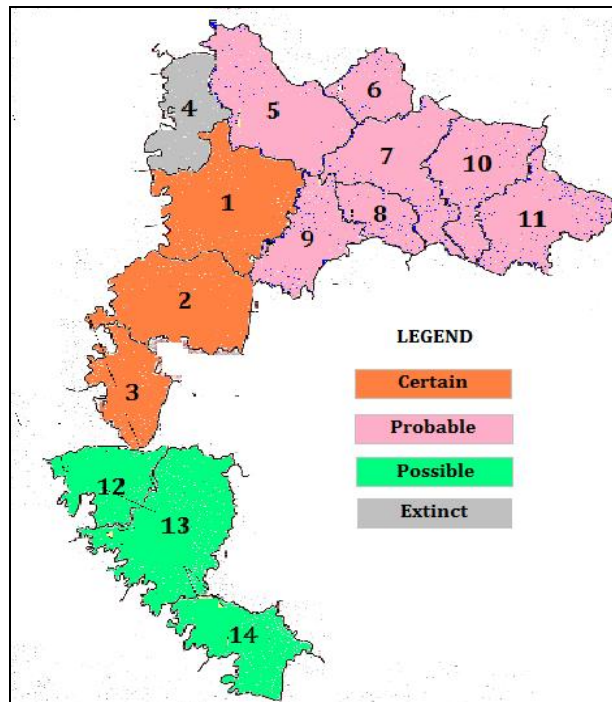
### **LAZAREVAC – STATE OF THE ENVIRONMENT AND NEPHROPATHY**

Lazarevac, one of the 17 municipalities with an area of 3,825 square kilometers, is located 55 kilometers southwest of Belgrade. This rather small municipality with 58,224 inhabitants (population census in 2011) attracted enormous public attention 90 years ago due to the discovery and progressive development of one of the endemic diseases – endemic nephropathy. Back in 1921/22 professor Danilović noted the presence of a curious nephrological disease hitherto insufficiently defined and poorly substantiated in literature. In the years after the war, namely 1956/57, the first thorough medical biochemical and other studies were done which confirmed the presence of nephropathy and led to the proclamation of the municipality of Lazarevac endemic. Extensive research on endemic nephritis had been started in the aforementioned area on the bank of Kolubara. Only in the period from 1972 to 1982 the far-reaching investigations on the ground revealed that out of 34 municipality settlements there was as many as 14 rural settlements where the disease was present, with particular emphasis placed on hyperendemic focal points – Šopić, Vreoci, Petka, Medoševac, Arapovac, Veliki Crljeni, Županjac, Dudovica, Junkovac, Čibutkovica, Sokolovo, Stepojevac and Cvetovac [5]. There had not been registered a single case of indigenous disease occurrence in the urban settlement of Lazarevac and the remaining 20 settlements. The location of the aforementioned rural communities indicates that it generally occurs in the areas affected by the work on surface exploitation of lignite. This fact has precisely what influenced the first analyses of the water, soil and air in the aforementioned settlements and the connection of these media with the households. By examining the literature we can see that the average annual concentration of basic pollutants (sulfur dioxide, nitrogen dioxide and soot) falls within the permissible limits, but what concerns is the data which show that among the specific pollutants benzo(a)pyrene significantly exceeds the limits. It is a polycyclic aromatic hydrocarbon which is produced by coal burning and has an extremely carcinogenic and toxic effects especially on people in the vicinity of a plant for processing and burning of coal. Maximum annual concentration allowed for C<sub>20</sub>H<sub>12</sub> amounts (1.0 ng / m<sup>3</sup>), while the deviations from the limit values have increased by 19.5% in 2009, by 55.2% in 2010 and by 55% in 2012. In the village of Vreoci (measuring stations "Toplana" and "Sušara") the increased concentration of nitrogen and

sulfur oxides has not been registered, but the concentration of soot has (0.54 to 2.2% above the threshold) as well as suspended particles of PM10 (26.2 to 93% above the limit values) for the period from 2011 to 2013 [6]. The quality control of the surface waters is carried out on the river of Peštan (right tributary of Kolubara) by the reference laboratory four times a year. The measuring station at Peštan shows that the water falls under class III in terms of the representation of suspended solids, dissolved O<sub>2</sub> values, and the percentage of O<sub>2</sub> saturation of water. In certain intervals the increased value of dissolved (Mn) was also registered. Saprobiological tests show that the watercourse is loaded with moderate organic pollution, in other words, that water quality corresponds to class II. The enormous amounts of waste water from households and industrial facilities also have negative implications for human health and the occurrence of nephritis. The villages in which primary and secondary sewerage networks lead to central septic tanks due to mining colonies, as well as direct discharge to the recipients: the rivers Onjeg (Dudovica and Čibutkovića), Peštan (Baroševac, Mali Crljeni and Rudovci) and the channel of Crna Bara (Veliki Crljeni). Industrial waste waters produced by the plants of the Electric Power Industry of Serbia ("Kolubara" mining basin, the branches of "Prerada", "Metal", thermal power plant "Kolubara A", "Površinski kopovi") in Vreoci, Veliki Crljeni, Baroševac, Rudovci and Cvetovac are purified, channeled and transported to the filtering plants, then discharged to the nearest streams. The waters are transported from the wastewater filtering plant to the river Kolubara via a 7 km long channel. During the course of 2011, 2012 and 2013, the amounts of filtered water discharged have been 504,000, 328,072 and 1,262,786 cubic metres respectively [7].

## **RESULTS OF RESEARCH AND DISCUSSION**

The cross-section study performed from 1971 to 1992 noted that, unlike other endemic areas, the municipality of Lazarevac was the only one that showed stability and even a relative increase in the incidence of the disease (approximately 80% of those in the chronic hemodialysis programme has got EN, and originates from the focal points). Realising the importance of new cases of the disease, the earlier field tests gave way to the more thorough clinical ones. Thus, the study conducted from 1993 to 2000 which involved 518 patients revealed high presence of endemic nephritis. As many as 218 patients were probably diagnosed with the disease, 49 of them surely had it, while 251 of them had all other kidney diseases. Looking at it individually, it was noted, however, that EN was the most common disease in the region [5].



**Figure 1.** Focal points of endemic nephropathy in Municipality of Lazarevac  
Settlements: 1–Vreoci, 2–Šopić, 3–Petka, 4–Cvetovac, 5–Veliki Crljeni, 6–Sokolovo,  
7–Junkovac, 8–Sakule, 9–Medoševac, 10–Arapovac, 11–Mirosaljci, 12–Županjac,  
13–Čibutkovica, 14–Dudovica

When it comes to some of the key characteristics of the patients in the municipality of Lazarevac, their monitoring revealed the following parameters [5,8]:

*Age of patients* – in the past, most patients were in the fifth and sixth decades, but since 1990 the threshold has extended, so the majority of them are in the group of patients in the seventh decade. The lowest incidence of the disease is in patients in the third decade of life, although one patient was younger than this limit (he was 21 and in an early clinical stage). On the other hand, the oldest patient was 80, but based on the consolidated data it was concluded that that the average age for all of the diseased was around  $56.61 \pm 14.7$  years. In the last 40 years this period had prolonged, thus in 1970 it was (51.6 years); from 1982 to 1991 (59.2 years), and from 1992 to 2001 (65 years). Years of experience led to the conclusion that EN has not been detected in a single child or adolescent, which only confirmed the professional literature theses dealing with this very curious phenomenon.

*Sex of patients* – in terms of gender representation, it can be said that EN equally affects men and women, and this relation is, in the majority of cases, 1.2:1 in favor of men.

*Mortality of patients* – the mortality rate used to be higher, as evidenced by the fact that in the period from 1966 to 1971 8.2 per 1,000 people died in the municipality of Lazarevac, while in the focal points that rate was even higher (Šopić – 9.3), (Petka – 8.2) and (Cvetovac – 10.8). The percentage of endemic nephropathy in the general mortality rate was even more pronounced, amounting from 30% in Cvetovac up to 41% in Šopić and Petka. Further progress of the treatment methods and less exposure to environmental influences caused the mortality rate to drop to 1.92 per 1,000 inhabitants.

Bearing in mind that the upper urothelial tumors (referring to the renal pelvis and ureter) and bladder tumors are more common in areas with endemic nephropathy (100 times as much in Serbia as in the endemic areas of Bulgaria and Romania), this disease was thoroughly researched in the region of Kolubara. Based on the monitoring, it was found that this group of malignant tumors were present in the municipalities of Lazarevac and Lajkovac, and its presence was at the highest level in the villages of Petka, Šopić and Cvetovac. It was then concluded that the risk for the population in endemic areas was as much as 95 times higher than for the residents of the other abovementioned municipalities [9]. It was found that the incidence is very high and amounts to 20.8 diseased per 1,000 inhabitants, while the rates themselves varied from 0.2 in Veliki Crljeni up to 18.7 in Petka, both belonging to the municipality of Lazarevac. One of the most complex study was carried out in the period from 1992 to 1994 within the Institute of Endemic Nephropathy, which included 73 patients diagnosed with urothelial tumors, while an identical number of diseased and treated from other kidney diseases was presented as a control group. The poll was conducted based on various categories (gender, age, marital status, family anamnesis, occupation, habits, etc.), which presented the basic postulates of patients who have been treated for the disease. Certain preliminary results of the conducted study were then presented: 67 percent of the patients suffering from endemic nephritis organizational had the presence of malignant TGU, 26.7 percent of the patients on dialysis at the Institute showed the presence of urothelial tumors, they occur in women more often than in men (1.4:1), age of the patients ranged from 50 to 80, but the largest number of affected was around 70 years old. All of them named farming as their primary or secondary occupation, smokers were affected 3 times more often than non-smokers and genetic factors are highlighted in the sense that in the first degree of consanguinity the risk of the emergence of TGU is as many as 21.8 times as higher [5].

### **THE ROLE OF TREATMENT IN ENDEMIC NEPHROPATHY**

After the confirmation of the disease most patients are included in the chronic hemodialysis programme. The inclusion of such patients in the chronic treatment programme started significantly later compared to other renal patients ( $63 \pm 8.0$  in relation to  $53 \pm 13.2$  years). However, the rehabilitation itself was much slower compared to other patients with CRF (chronic renal failure). The patients themselves were more often faced with the problem of anemia where the need for transfusions and additional iron was more common than in other patients. On the other hand, the most common and most dangerous complication of dialysis was gastrointestinal bleeding as a frequent cause of morbidity and mortality in the terminal stage of CRF, which resulted

from peptic ulcer disease (gastric and duodenal ulcers), erosive gastritis (damage to the stomach lining) or the use of non-steroidal anti-inflammatory drugs. The number of patients on hemodialysis is above 120 per year. Bearing in mind that the programme of hemodialysis includes mainly older people, the average number of years of this treatment was usually from 1 to 5, although there were also those who were exposed to this therapy over a period of 14-16 years [10]. Today, the implementer of this treatment is the Special Hospital for Endemic Nephropathy in Lazarevac founded in 1972, whose activity is directed to: the detection, prevention, suppression, treatment and rehabilitation of people suffering from endemic nephropathy, organization and improvement of the services which fight against endemic nephropathy, and scientific research in the area of endemic nephropathy. It is an institution of secondary character which performs activities to provide preventive, diagnostic, therapeutic and rehabilitative health methods in the fields of: internal medicine, nephrology, urology, endocrinology, nuclear medicine, medical biochemistry, interventional radiology and medical statistics. In order to perform all the activities, the institution employs 103 persons, of which 68.9 percent are medical staff, while 16.5 percent are medical doctors of various specialties. In order to address the thematic of endemic nephritis, the institution co-operates with numerous scientific research and health institutions in the country, as well as numerous professional associations [8].

## **CONCLUSION**

Based on all of the above, we can conclude that endemic nephropathy represents a major problem in the municipality of Lazarevac, which requires systematic analysis with the implementation of appropriate measures. We need to continue with further monitoring of environmental parameters and their association with the disease. In organizational terms, we should build a communal and wastewater filtering plant and work more on the prevention as much as possible. Therefore, we should strengthen the role of the Special Hospital for Endemic Nephropathy with the aim of early detection and treatment of the disease.

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