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A HISTORICAL OVERVIEW OF BALKAN ENDEMIC NEPHROPATHY (BEN) IN RELATION TO PUBLISHED HYPOTHESES

Nikola M. Pavlović

Clinic of Nephrology, Clinical Centre, Niš, Serbia,

Corresponding Author: Nikola Pavlović, Episkopska 38/23, 18000 Nis, Serbia, E-mail: nikpavster@gmail.com

Abstract

Balkan Endemic Nephropathy occurs with a high rate of prevalence in Serbia, Bulgaria, Romania, Bosnia and Herzegovina, and Croatia. The first cases described in Bulgaria, Serbia and Romania date to the late 1950s and early 1960s. BEN has been characterized to date as a chronic, slowly progressive familial tubular interstitial renal disease of unknown aetiology. The disease is characterized by its endemic nature, long incubation period, the familial clustering of the disease, and a exceptionally high incidence of upper urothelial tumour associated with BEN. To date several hypotheses have presented some findings that could be relevant to the etiology of BEN, but only one of them, chronic poisoning with Aristolochic acids, has provided convincing evidence related to BEN etiology and its clinical characteristics.

Key words: Balkan Endemic Nephropathy, Aristolochic acid, Genetic predisposition, Hypotheses.

Introduction

Balkan Endemic Nephropathy (BEN) occurs with a high rate of prevalence in Serbia, Bulgaria, Romania, Bosnia and Herzegovina, and Croatia [1, 2]. The first cases described in Bulgaria, Serbia and Romania date to the late 1950s and early 1960s. In 1956 firstly Tanchev et al. [3, 4] published the first detailed clinical description of the new disease entity in the Vratza region in Bulgaria. A renal disease with almost identical clinical and epidemiological characteristics was reported a year later, in Yugoslavia (Serbia), in the Lazarevac area [5]. It was found in 1961 that the similar nephropathy was also prevalent in Romania [6]. BEN has been characterized to date as a chronic, slowly progressive familial tubular interstitial renal disease of unknown aetiology [7]. The most prominent features of the disease are its endemic nature, long incubation period, the familial clustering of the disease and, remarkably, an unusually high incidence of upper urothelial tumour (UUT) associated with BEN or in the population [8, 9]. Following description of the first cases, the search to illuminate the etiology of BEN has been the topic of many studies producing the publication of several hypotheses. Although data published in relation to these hypotheses has presented some findings that could be relevant to the etiology of BEN, only one of them, chronic poisoning with Aristolochic acids (AA), has provided convincing evidence related to BEN's etiology and its clinical characteristics [10, 11].

Review of characteristics of Balkan Endemic Nephropathy

Diagnostic Criteria

The diagnosis of Balkan endemic nephropathy (BEN) used to be made using Danilovic's criteria [12]. However, later studies aimed at assessing their value in determining the prevalence, sensitivity, specificity, and predictive value found that Danilovic's criteria enabled the diagnosis of BEN in chronic renal failure only, and differential diagnosis between BEN and healthy persons but not between BEN and other

kidney diseases [13]. Proteinuria, urine alpha1-MG, kidney length and volume, were selected as significant predictors of BEN. Variables related to kidney failure, as well as several tubular disorders (urine specific gravity, Fractional sodium excretion (FENa) and Tubular phosphate reabsorption (TRP)), had an insignificant predictive value and could not be used for differential diagnosis of BEN [14]. The present diversity in applying diagnostic criteria for BEN stimulated the search for more universal criteria that would be acceptable for all research groups, and thus enable a comparison of the results gathered in different endemic areas. In order to achieve these goals the two meetings, the "International workshop on diagnostic criteria on BEN", held on Brač, Croatia in 2008, and at a meeting organized in 2012 (Skopje, R. Macedonia) were aimed at providing recommendations for the screening, diagnosing and therapy of patients with BEN.

Epidemiology

The researchers conducted several studies during the past decade aimed at determining the main epidemiological features of BEN in various endemic regions (Fig. 1), particularly in the most affected regions in Bulgaria, Romania and Serbia, in order to elucidate the controversial issue of whether BEN is tapering off or not [15, 16]. Although some studies published data

Figure 1 – Geographical distribution of BEN foci

indicating that BEN appears to be decreasing in incidence in the Bulgarian endemic regions [17, 18], the majority agree that in spite of occasional variations, the incidence of new cases remains stable over time [19, 20].

Pathology

Although data from systematic biopsy follow-up studies on the histology of BEN are still missing, rather sporadic biopsies done in different stages of BEN have provided some evidence about its pathology and enabled comparison with other well-established kidney disease entities and discussion of the etiology. Tubulo-interstitial changes are the most prevalent histological features obtained in pre-uraemic BEN patients (Fig. 2). Interstitial mostly scattered hypo cellular fibrosis accompanied by multifocal tubular atrophy, multifocal global glomerulosclerosis, arteriolosclerohyalinosis as well as arterial intimal fibroelastosis were the most frequent and more extensive in BEN patients than in age-matched control groups [21–23].

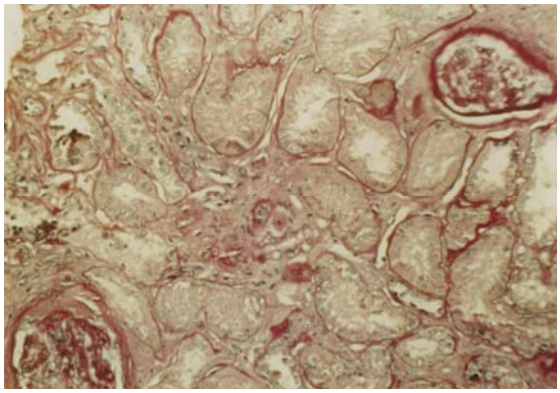

Figure 2 – Advanced glomerular sclerosis (initial obsolescence), with interstitial sclerosis and tubular atrophy in BEN patient (PAS, ×250). (Čukuranović R. Genetic and morphophysiologic study of Balkan endemic nephropathy. Doctoral Thesis. Medical Faculty: University of Niš: 1992: 1–169. [In Serbian])

Clinical Features

The first clinical classification of Balkan endemic nephropathy was elaborated by A. Puhlev et al. in 1960, according to the stages of the disease [24]. During the past more than fifty years, the clinical course of BEN has extended and has moved towards the older age in all endemic foci [25]. The clinical symptoms and signs of BEN are characterized by the initial long-lasting asymptomatic period. There is no fever, severe dysuria or other diseases preceding the onset of symptoms. In the advanced stages pallor of the skin and xanthochromia of palms and soles are noticeable. Blood pressure is normal, but in the advanced phases may be

elevated. Tubular type proteinuria may be found in early phases. Normo- or hypo-chromic normocytic hyporegenerative anaemia is a frequent finding. Urinary sediment presents with scarce white and red blood cells [26, 27]. In the end stage of renal failure, there is shrinkage of both kidneys to 3–4 cm in length [28]. One of the most peculiar characteristics of BEN is a strong association with upper urothelial tumours (UUT) [29].

Overview of the hypotheses

Lead Intoxication

In the first original paper on BEN published almost 50 years ago by Danilovic et al., lead was incriminated as causative agent of BEN, being found in flour used for making bread in affected villages [30]. However, this hypothesis was not substantiated by later studies.

Metals and Metalloids

In certain endemic areas, levels of Se deficiency approach those encountered in the Keshan province in China, where a severe cardiomyopathy linked to Se deficiency was endemic [31]. Some publications suggested the possibility that a deficiency of some essential trace elements, i.e. selenium, might be involved in the etiology of BEN [32]. However, no association of selenium deficiency with high incidence of BEN and UUC in endemic foci was confirmed. The similarity of lead and cadmium nephropathy to BEN indicated the need for valuation of the possibility that these nephrotoxic metals contribute to the production of the endemic renal disease [33].

Chronic Intoxication with Aristolochia Clematitis

In 1969, Ivić proposed that the etiology of BEN could be related to chronic Aristolochia clematitis poisoning (Fig. 3) in which seeds from these plants, which is encountered abundantly in local wheat fields, intermingle with wheat grain during the harvesting process [34]. He speculated that human exposure to a toxic component of Aristolochia might occur through ingestion of bread prepared from flour derived from contaminated grain. Ivic's well-documented experimental results and proposed hypothesis attracted more interest from the scientific community many years later. It followed the reports of a chronic renal disease that developed in a group of otherwise healthy Belgian women. It happened that in 1990, a clinic in Brussels began prescribing pills as part of a slimming regimen [35] consisting of Chinese herbal remedies intended to contain, in part, *Stephania tetrandra* (for its expected diuretic effects). Unintentionally, *S.tetrandra* (Han Fang-ji) was replaced by *A.fangchi* (Guang Fang-ji) since both plants are used in Chinese traditional medicine carrying similar names, *Fangji* [36]. The outbreak of a new disease entity, then called Chinese herbs nephropathy (CHN) in Belgium in 1993 affected more than 100 patients, mostly women, half of whom required renal replacement therapy [37].

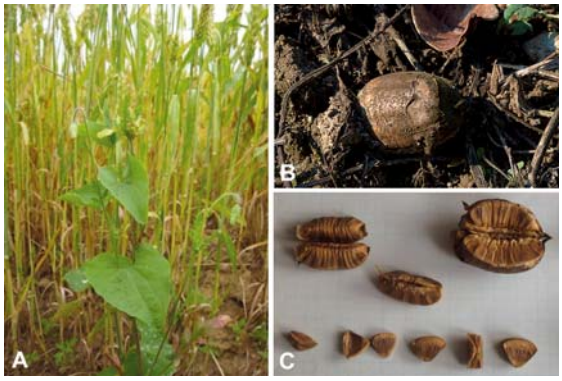

Figure 3 – Aristolochia Clematitis. A – Aristolochia Clematitis in the wheat field, B – Aristolochia Clematitis seeds in the soil, C – Aristolochia Clematitis ripe seeds

The CHN reported in Belgium in 1993 presented histologically as a rapidly progressive renal interstitial fibrosis leading to end-stage renal disease associated with a high risk of urothelial cancer [38, 39]. It was found that observed nephropathy, originally linked to the ingestion of Chinese herbal remedies that have accidentally included the *Aristolochia* species, is essentially caused by Aristolochic acid (AA) [40, 41] and is now called aristolochic acid nephropathy (AAN) [42].

Herbal remedies containing species of the genus *Aristolochia* were positively classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC) [43]. Aristolochic acids I (AA-I), and II (AA-II) are the most abundant of the aristolochic acids and are found in almost all *Aristolochia* species [44].

In 1994 Cosyns first pointed out that the unique renal histopathology lesions of so-called CHN are strikingly similar to those described in BEN. The clinical presentation of the patients was also similar to that observed in BEN: normal blood pressure, aseptic leukocyturia, low grade low molecular weight proteinuria, early and severe anaemia. On morphological and clinical grounds, CHN appeared similar to BEN, and a common etiologic agent, aristolochic acid, was suspected for the first time [45].

Similarities of CHN to BEN that have led to the hypothesis of a common etiological agent for both diseases prompted some researchers to produce an important projection; namely, that BEN, CHN, and AAN are the same disease [46–49], and on the other hand, dietary ingestion of AA [50, 51], in conjunction with individual genetic susceptibility, accounts for all the epidemiological, clinical and pathophysiological features of BEN and attendant UUC (Fig. 4).

Figure 4 – Kidney international, cover page. (Reprinted by permission of Macmillan Publishers Ltd: Kidney International, 81, copyright 2012)

A recent publication by Grollman et al. presented the results showing that the accumulation of AL-DNA adducts was present in the renal cortex and upper urinary tract of patients with BEN from an endemic region in Croatia, but not in patients with other forms of chronic renal disease or patients with upper urinary tract transitional cell cancer living in a nonendemic area of Croatia [52]. The finding that AA-derived DNA adducts in renal cortical and urothelial tumor tissue of patients with documented BEN, associated with the dominance of the A:T $\rightarrow$ T:A transversions in the p53 tumour suppressor gene mutational spectrum, was essential in the identification of AA as an etiological agent of the upper tract malignancy observed in BEN [53].

Importantly, a molecular epidemiologic study undertaken to explore the proposition that AA contributes significantly to the high incidence of UUT in Taiwan strongly supported the hypothesis that all components of the AA signature TP53 mutational spectrum, established in the context of UUT associated with BEN, are present in Taiwanese patients with UUT [54].

Ochratoxin A

Finding that porcine nephropathy has many characteristics in common with BEN led some researchers to propose that ochratoxin A induced renal disease and urothelial tumours in humans is very likely. It was one of the first well elaborated hypotheses regarding the etiology and pathogenesis of BEN that appeared in the literature in the early 1970s [55]. Ochratoxin A is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals. However, no adequate human studies of the relationship between exposure to ochratoxin A and human renal disease and cancer have been reported.

Pliocene Lignite

This hypothesis was proposed in 1991 [56] based on the geographical overlapping between the location of Pliocene lignite deposits in the Balkans and the location of endemic areas, as well as analyses of well water from endemic villages in former Yugoslavia, which showed the presence of organic compounds in higher concentrations than in well water from nonendemic villages [57].

The lignite hypothesis is based on the assumption that toxic organic compounds in lignite, or in weathered lignite, may be leached by groundwater and thus contaminate drinking water wells supplied by this groundwater. Although the concentrations of these organic molecules in the well water may be low, long expo-

sure and/or accumulation in body tissues over time may lead to kidney lesions. The development of urothelial carcinomas in some individuals can also be explained by this hypothesis because most of these toxic organics are well-known carcinogenic factors [58–60].

Genetic Predisposition

The familial clustering of the disease was right from the beginning indicative of the role of genetic predisposition in the etiology of BEN and prompted many genetic investigations [61].

The hypothesis implicating the multifactor nature of BEN etiology assumes that genetic factors create a predisposition to BEN [62].

Changes in Enzyme Activity

Norum and Gjone described familial deficiency of lecithin-cholesterol acyltransferase (LCAT) in 1967 as a primary disorder. They showed that familial renal disease can develop secondary to LCAT deficiency and associated lipid abnormalities [63]. It was found by Pavlovic in 1991 that a certain proportion of healthy subjects from BEN families have a peculiar form of lipid abnormalities associated with an abnormally low LCAT activity, and a possible association between these abnormalities and the etiology of BEN was raised for the first time [64].

Genetic Polymorphism

Numerous studies conducted in experimental settings and BEN patients investigated the role of several genetic polymorphisms in many enzymes (CYP2D6, CYP3A4, CYP3A5, NQO1, GSTT1, GSTM1, GSTP1, NAT1 and NAT2) from a detoxification system [65–67]. It has been shown that genetic variants of these enzymes involved in the uptake, conversion and excretion of xenobiotics determine individual levels of detoxification and are modifiers of an increased/decreased risk of chronic diseases and/or cancer [68, 69].

Chromosomal Aberrations

A hypothesis was put forward that the occurrence and frequent association of BEN and cancer can be explained by the chromosomal hypothesis of oncogenesis. The first cytogenetic investigation of healthy relatives of patients with BEN who were born in nonendemic areas was done in 1985 [70].

Finding of a specific chromosome marker 3q in BEN was reported, characterized by a discordance in the banding patterns of the long arms, shortening the band 3q25, faster fusion of sub-bands q26.1 and q26.3 and lack of differentiation of q24 [71].

Viral Disease

Although some promising evidence of viral involvement in the etiology in BEN was published in 1975, suggesting that a slow corona virus infection causes endemic nephropathy in man [72], data substantiating this hypothesis remained unconvincing [73, 74].

Immunological Changes

The authors performed this study to evaluate the possible correlation of BEN with the polymorphism of the Ig heavy chain 3' Regulatory Region enhancer hsl. 2 that is related to changes of consensus for trans activators binding within the DNA sequence and probably consequently autoimmune and inflammatory diseases. The allelic frequencies of hsl. 2 of BEN patients and family members had a similar decrease frequency of allele *1 and increase of allele *2 with respect to the controls. This trend suggests the association of allele *1 as a protective and allele *2 as a risk component for the disease. The presence of a consensus sequence for NF-Kb in the allele *2 may link the polymorphism to the inflammatory activity of BEN. This study supports the presence of an inflammatory pathway in BEN through the involvement of polymorphic enhancer hsl. 2 influencing differently binding complexes and consequently the 3D structure of 3' Regulatory Region of IgH. This work is the first study that clearly links BEN to a gene involved in the regulation of immune response [75].

Miscellaneous-Multifactorial Etiologies

In this study, the authors proposed new hypotheses on the possible relationship between the Pliocene lignite and decreased LCAT activity in the etiology of BEN. They examined the influence of soluble organic compounds in drinking water on plasma LCAT activity.

The possible simultaneous role of coal-derived toxic organic compounds and decreesed enzyme LCAT activity in the etiology of BEN using water concentrates from both endemic and non-endemic areas was tested by Pavlovic et al. [76]. It has been shown that well water from BEN villages contains higher numbers and concentrations of both extractable and high molecular weight organic compounds compared to controls. The study presented the results that support the new multifactor hypothesis of BEN etiology. Namely, water samples from BEN villages from Serbia and Romania showed higher LCAT inhibiting activity compared to deionised water.

Conclusions

On the grounds of all these previously published hypotheses we can conclude:

1. The idea that the multifactorrial etiology of BEN is the hallmark of the disease and genetic predisposition is an unavoidable factor for the development of BEN.

2. Genetic predisposition is presumably responsible for providing the key circumstances for imposing the action of environmental endogenous etiological factors.

3. The presence of the worldwide distribution of *Aristolochia* spp. Along with widespread use of herbal remedies in traditional Chinese medicine, and recently published data that some crops can take up AA from the soil (77), there is the possibility that diseases similar to BEN and UUC exist elsewhere as unrecognized disease entities. This could be the case with a group of unknown renal diseases in ERA-EDTA Registry (Fig. 5).

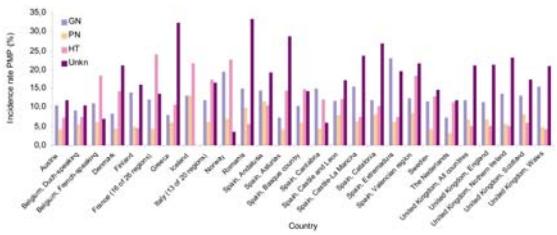

Figure 5 – Incident rates per million population, unadjusted at day 1, by cause of renal failure, ERA-EDTA, Annual report 2008

4. Although over the past more than 50 years we have witnessed the publication of various hypotheses, only one of them, chronic poisoning with AA, has provided convincing evidence relating to BEN etiology and its clinical and epidemiological characteristics.

5. Many scientists in the world dealing with projects aimed at investigating nephrotoxic and cancerogenic effects of AA use, with the utmost confidence, the equation CHN= AAN=BEN.

6. It seems reasonable to accept with the highest certainty that the etiology of BEN and attendant UUT have been eventually solved, and that BEN and UUT are not only confined to the Balkans but could be found anywhere in the world [78]. Thus, AAN and BEN become a worldwide problem [79].

REFERENCES

1. Stefanović V, Polenaković M. Fifty years of research in Balkan endemic nephropathy: where are we now? Nephron Clin Pract. 2009; 112(2): c51–c56.
2. Danilovic V. Endemic nephropathy in Yugoslavia. In: Strahinjic S, Stefanovic V (eds). Endemic (Balkan) Nephropathy, Proceedings of the 4th Symposium on Endemic (Balkan) Nephropathy, Nis 1979. Nis: Inst Nephr Haemod. 1981: 1–5.
3. Tanchev Y, Evstatiev Z, Dorossiev D, et al. Studies on the nephritides in the District of Vratza. Savremenna Medicina. 1956; 7(9): 14–29.
4. Tanchev Y, Dorossiev D. The first clinical description of Balkan endemic nephropathy (1956) and its validity 35 years later. IARC Sci Publ. 1991; 115: 21–28.
5. Danilović V, Djurišić M, Mokranjac M, et al. Nephrites chroniques provoquees par l'intoxication au plomb par voie digestive (farine). Presse Med. 1957; 65: 2039–2040.
6. Fortza N, Negoescu M. Nefrita cronica azotemia endoepidemica. Stud Cercet Med. 1961, 1: 217–221.
7. Ferluga D, Hvala A, Vizjak A, et al. Renal function, protein excretion, and pathology of Balkan endemic nephropathy. III. Light and electron microscopic studies. Kidney Int. 1991; 40(Suppl 34): S57–S67.
8. Radovanović Z, Janković S, Jevremović I. Incidence of tumors of urinary organs in a focus of Balkan endemic nephropathy. Kidney Int. 1991; 34: S75–S76.
9. Nikolic J, Djokic M, Ignjatovic I, Stefanovic V. Upper urothelial tumors in emigrants from Balkan endemic nephropathy areas in Serbia. Urol Int. 2006; 77(3): 240–244.
10. Arlt VM, Stiborova M, Schmeiser HH. Aristolochic acid as a probable human cancer hazard in herbal remedies: a review. Mutagenesis. 2002 17: 265–277.
11. Grollman AP, Jelaković B. Role of environmental toxins in endemic (Balkan) nephropathy. October

2006, Zagreb, Croatia. J Am Soc Nephrol. 2007; 18(11): 2817–2823.
12. Stefanovic V, Jelakovic B, Cukuranovic R, et al. Diagnostic criteria for Balkan endemic nephropathy: proposal by an international panel. Ren Fail. 2007; 29(7): 867–880.
13. Djukanović L, Marić I, Marinković J, et al. Evaluation of criteria for the diagnosis of Balkan endemic nephropathy. Ren Fail. 2007; 29(5): 607–614.
14. Djukanović L, Marinković J, Marić I, et al. Contribution to the definition of diagnostic criteria for Balkan endemic nephropathy. Nephrol Dial Transplant. 2008; 23(12): 3932–3938.
15. Janković S, Bukvić D, Marinković J, et al. Time trends in Balkan endemic nephropathy incidence in the most affected region in Serbia, 1977–2009: the disease has not yet disappeared. Nephrol Dial Transplant. 2011; 26(10): 3171–3176.
16. Stefanovic V, Cukuranovic R, Miljkovic S, et al. Fifty years of Balkan endemic nephropathy: challenges of study using epidemiological method. Ren Fail. 2009; 31(5): 409–418.
17. Plamen S. Dimitrov, Valeri A, et al. Balkan endemic nephropathy in Vratza, Bulgaria, 1964–1987: An epidemiologic analysis of population-based disease registers. Eur J Epidemiol. 2001; 17(9): 847–853.
18. Cukuranovic R, Petrovic B, Cukuranovic Z, Stefanovic V. Balkan endemic nephropathy: a decreasing incidence of the disease. Pathol Biol (Paris). 2000; 48(6): 558–561.
19. Dimitrov PS, Simeonov VA, Ganev VS, Karmaus WJ. Is the incidence of Balkan endemic nephropathy decreasing? Pathol Biol (Paris). 2002; 50(1): 38–41.
20. Janković S, Bukvić D, Marinković J, et al. Trends in incidence and prevalence of balkan endemic nephropathy in the three most affected villages in serbia over a 36-year period. Ren Fail. 2013; 35(4): 509–513.
21. Ferluga D, Hvala A, Trnačević S, et al. Pathology of Balkan endemic nephropathy – A correlation with established kidney disease entities. Facta Universitatis Series: Medicine and Biology 2002; 9(1): 82–87.
22. Mandal AK, Sindjic M, Sommers SC. Kidney pathology in endemic nephropathy. Clin Nephrol. 1987; 27(6): 304–308.
23. Čukuranović R. [Genetic and morphophysiologic study of Balkan endemic nephropathy]. Doctoral Thesis. Medical Faculty, University of Niš: 1992: 1–169, 1992 [In Serbian].
24. Dimitrov Ts. [Clinical and morphologic stages in Balkan endemic nephropathy]. Vutr Boles. 1983; 22(6): 69–72. [Article in Bulgarian].
25. Djukanović L, Stefanović V, Basta-Jovanović G, et al. [Investigation of Balkan endemic nephropathy in Serbia: how to proceed?]. Srp Arh Celok Lek. 2010; 138(3–4): 256–261. [Article in Serbian].
26. Radonić M, Radosević Z. Clinical features of Balkan endemic nephropathy. Food Chem Toxicol. 1992; 30(3): 189–192.
27. Polenakovic M, Stefanovic V. Balkan Nephropathy. In: Davison A, Cameron JS, Kerr DN, Ritz E, Winearls Ch (eds). Oxford Textbook of Clinical Nephrology, Oxford: Oxford University Press: 1998: 1202–1210.
28. Vukelic M, Sostaric B, Belicza M. Pathomorphology of Balkan endemic nephropathy. Food Chem Toxicol. 1992, 30(3): 193–200.
29. Stefanovic V, Polenakovic M, Toncheva D. Urothelial carcinoma associated with Balkan endemic nephropathy. A worldwide disease. Pathol Biol (Paris). 2011; 59(5): 286–291.
30. Danilovic V, Djurisic M, Mokranjac M, et al. [Familial kidney diseases in the village Sopic caused by chronic lead poisoning]. Srp Arh Celok Lek. 1957; 85(10): 1115–1125.
31. Fuyu Y. Keshan disease and mitochondrial cardiomyopathy. Sci China C Life Sci. 2006; 49(6): 513–518.
32. Maksimović ZJ. Selenium deficiency and Balkan endemic nephropathy. Kidney Int Suppl. 1991; 34: S12–S14.
33. Wedeen RP. Environmental renal disease: lead, cadmium and Balkan endemic nephropathy. Kidney Int Suppl. 1991; 34: S4–S8.
34. Ivić M. Etiology of endemic nephropathy. Lijec Vjesn. 1969; 91: 1273–1281.
35. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: Association with slimming regimen including Chinese herbs. Lancet. 1993; 341(8842): 387–391.
36. Vanherweghem JL. Misuse of herbal remedies: the case of an outbreak of terminal renal failure in Belgium (Chinese herb nephropathy). J Altern Complement Med. 1998; 4: 9–13.
37. Vanherweghem JL. A new form of nephropathy secondary to the absorption of Chinese herbs. Bull Mem Acad R Med Belg. 1994; 149(1–2): 128–135; discussion 135–140 (in French).
38. Cosyns JP, Jadoul M, Squifflet JP, et al. Urothelial lesions in Chinese-herb nephropathy. Am J Kidney Dis. 1999; 33: 1011–1017.
39. Nortier JL, Vanherweghem JL. Renal interstitial fibrosis and urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). Toxicology. 2002; 181–182: 577–580.
40. Schmeiser HH, Bieler CA, Wiessler M, et al. Detection of DNA adducts formed by aristolochic acid in renal tissue from patients with Chinese herbs nephropathy. Cancer Res.1996; 56(9): 2025–2028.

41. Bieler CA, Stiborova M, Wiessler M, et al. 32P-post-labelling analysis of DNA adducts formed by aristolochic acid in tissues from patients with Chinese herbs nephropathy. Carcinogenesis. 1997; 18(5): 1063–1067.
42. Cosyns JP. Aristolochic acid and 'Chinese herb nephropathy': a review of the evidence to date. Drug Saf. 2003; 26(1): 33–48.
43. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monogr Eval Carcinog Risks Hum. 2002; 82: 1–556.
44. Cosyns JP, Jadoul M, Squifflet JP, et al. Chinese herbs nephropathy: A clue to Balkan endemic nephropathy? Kidney Int. 1994; 45(6): 1680–1688.
45. Grollman AP, Jelaković B. Role of environmental toxins in endemic (Balkan) nephropathy. October 2006, Zagreb, Croatia. J Am Soc Nephrol. 2007; 18(11): 2817–2823.
46. Grollman AP, Shibutani S, Moriya M, et al. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. Proc Natl Acad Sci U S A 2007; 104(29): 12129–12134.
47. De Broe E. Chinese herbs nephropathy and Balkan endemic nephropathy: toward a single entity, aristolochic acid nephropathy. Kidney Int. 2012. 81, 513–515.
48. Arlt VM, Stiborová M, vom Brocke J, et al. Aristolochic acid mutagenesis: molecular clues to the aetiology of Balkan endemic nephropathy-associated urothelial cancer. Carcinogenesis. 2007; 28(11): 2253–2261.
49. Grollman AP, Scarborough J, Jelaković B. Aristolochic acid nephropathy: An environmental and iatrogenic disease. In: Fishbein J (ed). Advances in molecular toxicology 3, Elsevier: Amsterdam: 2009: 211–222.
50. Hranjec T, Kovac A, Kos J, et al. Endemic nephropathy: the case for chronic poisoning by aristolochia. Croat Med J. 2005; 46: 116–125.
51. Grollman AP, Shibutani S, Moriya M, et al. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. Proc Natl Acad Sci USA. 2007; 104: 12129 – 12134.
52. Slade N, Moll UM, Brdar B, et al. p53 mutations as fingerprints for aristolochic acid: an environmental carcinogen in endemic (Balkan) nephropathy. Mutat Res. 2009; 663(1–2): 1–6.
53. Chen CH, Dickman KG, Moriya M, et al. Aristolochic acid-associated urothelial cancer in Taiwan. Proc Natl Acad Sci USA. 2012; 109: 8241–8246.
54. Krogh P, Hald B, Plestina R, Ceović S. Balkan (endemic) nephropathy and foodborn ochratoxin A: Preliminary results of a survey of foodstuffs. Acta Pathol Microbiol Scand B. 1977; 85: 238–240.
55. Feder GL, Radovanović Z, Finkelman RB. Relationship between weathered coal deposits and the etiology of Balkan endemic nephropathy. Kidney Int Suppl. 1991; 34: S9–S11.
56. Orem WH, Feder GL, Finkelman RB. A possible link between Balkan endemic nephropathy and the leaching of toxic organic compounds from Pliocene lignite by groundwater: preliminary investigation. Int J Coal Geol. 1999; 40: 237–252.
57. Feder GL, Tatu CA, Orem WH, et al. Weathered coal deposits and Balkan endemic nephropathy. Facta Universitatis Series Medicine and Biology 2001; 9(1): 34–38.
58. Orem WH, Tatu CA, Lerch III HE, et al. Identification and environmental significance of the organic compounds in water supplies associated with a Balkan endemic nephropathy region in Romania. J Environ Health Res. 2004; 3(2): 53–61.
59. Orem W, Tatu C, Pavlovic N, et al. Health effects of toxic organic substances from coal: toward "panendemic" nephropathy. Ambio. 2007; 36(1): 98–102.
60. Toncheva D, Dimitrov T. Genetic predisposition to Balkan endemic nephropathy. Nephron. 1996; 72(4): 564–569.
61. Toncheva D, Dimitrov T, Stojanova S. Etiology of Balkan endemic nephropathy: a multifactorial disease? Eur J Epidemiol. 1998; 14: 389–394.
62. Norum KR, Gjone E. Familial serum-cholesterol esterification failure. A new inborn error of metabolism. Biochim Biophys Acta. 1967; 144(3): 698–700.
63. Pavlović NM, Varghese Z, Persaud JW, et al. Partial lecithin: cholesterol acyltransferase (LCAT) deficiency in Balkan endemic nephropathy. Kidney Int Suppl. 1991; 34: S102–S104.
64. Atanasova SY, von Ahsen N, Toncheva DI, et al. Genetic polymorphisms of cytochrome P450 among patients with Balkan endemic nephropathy (BEN). Clin Biochem. 2005; 38(3): 223–228.
65. Andonova IE, Sarueva RB, Horvath AD, et al. Balkan endemic nephropathy and genetic variants of glutathione S-transferases. J Nephrol. 2004; 17(3): 390–398.
66. Toncheva DI, Von Ahsen N, Atanasova SY, et al. Identification of NQO1 and GSTs genotype frequencies in Bulgarian patients with Balkan endemic nephropathy. J Nephrol. 2004; 17(3): 384–389.
67. Ozawa S. [Genetic polymorphisms in xenobiotic metabolizing enzymes as a determinant of susceptibility to environmental mutagens and carcinogens in humans]. Yakugaku Zasshi. 1997; 117(10–11): 895–909 [Article in Japanese].
68. Wolf CR. Individuality in cytochrome P450 expression and its association with the nephrotoxic and carcinogenic effects of chemicals. IARC Sci Publ. 1991; (115): 281–287.

69. Tsoneva M, Dimitrov Ts, Toncheva D. [Familial cytogenetic studies in Balkan endemic nephropathy]. II. Vutr Boles 1985; 24(5): 61–66 [Article in Bulgarian].
70. Toncheva D, Dimitrov T, Tzoneva M. Cytogenetic studies in Balkan endemic nephropathy. Nephron. 1988; 48(1): 18–21.
71. Apostolov K, Spasic P. Evidence of a viral aetiology in endemic (Balkan) nephropathy. Lancet. 1975; 2(7948): 1271–1273.
72. Uzelac-Keserović B, Spasić P, Bojanić N, et al. Isolation of a coronavirus from kidney biopsies of endemic Balkan nephropathy patients. Nephron. 1999; 81: 141–145.
73. Riquelme C, Escors D, Ortego J, et al. Nature of the virus associated with endemic Balkan nephropathy. Emerg Infect Dis. 2002; 8: 869–870.
74. Frezza D, Serone E, Lolli S, et al. Balkan Endemic Nephropathy risk associates to the hs1,2 Ig enhancer polymorphism. Eur J Inflamm. 2012; 10(3): 393–403.
75. Pavlovic NM, Orem WH, Tatu CA, et al. The role of lecithin cholesterol acyltransferase and organic substances from coal in the etiology of Balkan endemic nephropathy: a new hypothesis. Food Chem Toxicol. 2008; 46(3): 949–954.
76. Pavlović NM, Maksimović V, Maksimović JD, et al. Possible health impacts of naturally occurring uptake of aristolochic acids by maize and cucumber roots: links to the etiology of endemic (Balkan) nephropathy. Environ Geochem Health. 2013; 35(2): 215–226.
77. Gökmen MR, Cosyns JP, Arlt VM, et al. The epidemiology, diagnosis, and management of aristolochic Acid nephropathy: a narrative review. Ann Intern Med. 2013; 158(6): 469–477.
78. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. Kidney Int. 2008; 74(2): 158–169.

Резиме

ИСТОРИСКИ ПРЕГЛЕД НА БАЛКАНСКАТА ЕНДЕМСКА НЕФРОПАТИЈА (БЕН) ВО ОДНОС НА ОБЈАВЕНИТЕ ХИПОТЕЗИ

Никола М. Павловиќ

Клиника за нефрологија, Клинички центар, Ниш, Србија

Балканската ендемска нефропатија се јавува со висока стапка на превалентност во Србија, Бугарија, Романија, Босна и Херцеговина и во Хрватска. Првите случаи беа опишани во Бугарија, Србија и во Романија кон крајот на 1950-тите и почетокот на 1960-тите години. До денес БЕН се карактеризира како хронична, бавно прогресивна фамилијарна тубуларна интерстицијална бубрежна болест со непозната етиологија. Болеста се карактеризира со свој ендемски карактер, долг период на инкубација, фамилијарно гру-пирање на болеста, како и исклучително висока инциденца на горниот уротелијален тумор поврзан со БЕН. До денес неколку хипотези презентирале одредени наоди кои би можеле да бидат релевантни за етиологијата на БЕН, но само една од нив, хронично труење со аристолохична киселина, има обезбедено убедливи докази поврзани со етиологијата на БЕН и нејзините клинички карактеристики.

Клучни зборови: балканска ендемска нефропатија, аристолохична киселина, генетската предиспозиција, хипотези.