



## BALKAN ENDEMIC NEPHROPATHY. A REAPPRAISAL AFTER FORTY YEARS

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**Summary.** *Balkan endemic nephropathy (BEN) was described in 1957, and this review gives an account of research forty years later. The etiology remains the main unanswered problem in BEN despite broad investigations conducted into the possible role of genetic factors, environmental agents and immune mechanisms. The evidence accumulated so far indicates that BEN is an environmentally-induced disease. A continuous, but cyclic, effect of environmental factors upon kidneys of children from the endemic settlements and endemic families in particular was demonstrated. Weathering of low-rank coals nearby the endemic villages produces water soluble polycyclic aromatic hydrocarbons and aromatic amines, similar to metabolic products of acetaminophen that has a causal relationship with analgesic nephropathy. Many of these compounds are known to be carcinogenic and could also cause urothelial cancer. The similarity of the morphological and clinical pattern of BEN and Chinese herb nephropathy has raised the possibility of a common etiologic agent, aristolochic acid. Genetic studies have landed support for genetic predisposition to BEN.*

*Kidney morphology in early stages of the disease is peculiar and resembles that of aging with pronounced renal vascular changes. The histopathology is predominantly tubulointerstitial sclerosis without infiltrates. Humoral immune mechanisms do not appear to play a pathogenic role in BEN.*

*An increased incidence of tumors of renal pelvis and ureter in patients with BEN and in population from endemic settlements has been observed. Recently the frequency of urinary bladder tumors in endemic settlements was also found increased compared with the nonendemic villages and cities. The geographic correlation between BEN and urinary tract tumors supports the speculation that these diseases share a common etiology.*

**Key words:** *Balkan endemic nephropathy, urothelial cancer, etiology, prevention*

### Introduction

Balkan endemic nephropathy (BEN) is a chronic tubulointerstitial kidney disease encountered in high rate among the population of settlements along the tributaries of the Danube River in Serbia, Bosnia, Croatia, Bulgaria and Rumania.

BEN was described in 1957, and in the last forty years much has been done in the understanding of this disease. Investigations were directed to the epidemiology, etiology, morphology and treatment of BEN. Results of these studies were reviewed elsewhere (1-4).

We would like to present a survey of the recent studies and a preview of future research. Major emphasis will be given to the etiology, morphogenesis, and associated urothelial cancer.

### Environmentally induced disease

The evidence accumulated indicated that BEN is an

environmentally induced disease. In the first paper on BEN by Danilović et al. (1957) lead was considered the causal agent of BEN, being found in flour used for making bread in affected settlements (5). At the time lead was used to repair cracks in the mill wheels, contaminating the flour. However, this hypothesis was not substantiated by further studies. In patients with BEN lead excretion was not found different from urinary excretion in control population. Gaon et al. (1962) performed CaNa<sub>2</sub> EDTA lead mobilization tests in 31 patients with BEN. The maximum daily lead-chelate excretion was 530 µg and the mean three-day lead-chelate excretion was 192 µg, being in the limits of normal (6). Urine and blood concentrations may be inadequate measures of low-level environmental exposure (7). However, BEN and lead nephropathy have several different features. Similar to BEN lead nephropathy is characterized by a latency of 3-30 years, however marked hypertension, gout and neuro-behavioral disturbances are characteristic for lead

nephropathy, and not observed in BEN. The absence of familial occurrence, low-molecular weight (LMW) proteinuria or association with urinary tract tumours in lead poisoning further distinguishes these two nephropathies (8,9).

Cadmium was found increased in soil, water and food from endemic regions (10). Cadmium produces a chronic Fanconi syndrome characterized by LMW proteinuria and urinary calcium wasting. Renal failure is uncommon but severe osteomalacia characterized by painful bone lesions/pseudofractures and renal stone diseases develop. Industrial cadmium pollution of several rivers in Japan was found to have caused contamination of the local rice (11). The disease known in Japanese as "itai-itai" or "ouch-ouch" is easily distinguished from BEN. Measurements of urinary cadmium in women from BEN villages have revealed an excretion of less than 1.26  $\mu\text{g/g}$  creatinine, while in itai-itai disease the average excretion was 10  $\mu\text{g/g}$  creatinine (12).

There is also the possibility that a deficiency of some essential trace element, i.e. selenium, might be involved in the etiology of BEN (13). Selenium has been demonstrated as an integral part of glutathione peroxidase (GSH-Px), an enzyme which catalyses the reduction of lipid hydroperoxides and hydrogen peroxide. GSH-Px activity in BEN patients was significantly decreased, comparing to the healthy control, however, similar to the enzyme activity in some other renal failure patients. In healthy family members of BEN patients GSH-Px activity was about the same as in control group (14). Selenium deficiency has been associated with cardiac disease in China, but there has been no association with renal disease. Selenium deficient areas were found in many countries, and it is unlikely that selenium plays a role in the pathogenesis of BEN.

The effect of environmental factors is important for the developing kidney, therefore a study on the possible effect of these factors was performed in children from endemic settlements, non-endemic villages and large cities (15). Estimation of the effect of environmental factors was made by determining several markers of glomerular and tubular functions. As the effect of environmental factors is associated with seasonal variations, this study was performed in different seasons (autumn, winter and spring) during a three-year period. It has shown a significant effect of the environmental factors upon the kidney of schoolchildren in endemic settlements, and especially in families burdened with BEN. The effect of environmental factors was recorded in all seasons investigated, and in particular in autumn (October). It was shown that in children urinary  $\beta_2$ -microglobulin, albumin and N-acetyl glucosaminidase (NAGA) are sensitive indicators of kidney damage induced by the toxic factors from the environment.

Feder et al. studied the geochemistry of the areas where the disease is endemic (16). They found that endemic settlements are located near weathered coal deposits. Most endemic foci have Pliocene age lignites

in their vicinity. Pliocene age coals are 1.6 to 5.3 million years old and are the youngest coals in the Balkans. These low-rank coals in the Balkans still retain many of the complex organic compounds contained in the decaying plant precursors of the coal. Weathering of the low-rank coals could generate complex mixtures of water-soluble hydrocarbons, which are present in the drinking water of the shallow farm wells. Preliminary results from qualitative chemical analyses of drinking water from shallow farm wells in endemic settlements indicate the presence of soluble polar polycyclic aromatic hydrocarbons and aromatic amines, for example naphthylamine, aniline, anthracene, pyrene. Many of these compounds are known to be carcinogenic and could also cause urothelial cancer. This natural contamination may combine with numerous sources of man-made pollution common in both the endemic and control villages to provide the factor or co-factors responsible for the disease.

Several cases of end-stage interstitial kidney disease have been recently reported in young women who have been on the slimming regimen including Chinese herbs (17). Aristolochic acid was isolated from several batches of pills, accidentally delivered as powder of *Aristolochia fangchi*, in place of non-toxic *Stephania tetrandra* (18). Several characteristics of this nephropathy have been described: development of end-stage kidney disease in within 1-2 years, normal arterial blood pressure, extensive interstitial fibrosis, LMV proteinuria, urothelial atypias and malignancy (19). The similarity of the morphology and clinical features of Chinese herbs nephropathy and BEN has raised the possibility of a common etiologic agent, aristolochic acid (20). Some 25 years ago aristolochic acid was suggested as the etiologic agent of BEN. Ivić has found aristolochic acid in flour obtained from wheat contaminated with seeds of *Aristolochia clematis* in endemic region (21). He conducted a survey of the geographical distribution of the plant, *Aristolochia clematis*, in the endemic area. This plant performs both, the nephrotoxic and cancerogenic action. Focal tubulointerstitial changes were observed in rabbits poisoned by giving them orally various amounts of flour made from ground dried *Aristolochia* seeds. These changes corresponded completely to the changes characteristic of BEN.

Ochratoxin A is a mycotoxin demonstrated to be responsible for porcine nephropathy in northern Europe (22). Porcine nephropathy is primarily a tubulointerstitial disease similar to BEN in many ways, suggesting a common causal relationship. The most pronounced food-borne exposure to ochratoxin has been found in the area in Croatia where BEN is prevalent (23). The associated nephrotoxicity and carcinogenicity of ochratoxin A recently described make this hypothesis particularly attractive. However, the fact that nonendemic as well as endemic regions have ochratoxin contamination raises doubts about the primary role of this mycotoxin in the etiology of BEN. Indeed, to date

there is no evidence that ochratoxin is responsible for any kidney disease in humans.

### Genetic predisposition to BEN

A familial aggregation of BEN has been described forty years ago (5). Development of BEN in emigrants from the endemic region, who left their native villages in early childhood and settled hundreds, sometimes thousands of miles away, is in support of the role of the inheritance in the development of BEN (23). A study in the region of Slavonski Brod, Croatia, has revealed the inheritability of BEN of 24.5 (24). In BEN patients and healthy controls the frequency of 20 randomly selected morphophysiological properties controlled by one or a few genes with alternative dominant or recessive mode of expression were compared. Statistically significant differences were found in 5/20 morphophysiological properties analyzed, and it was concluded that these two groups differ approximately in 25% of allelogenes (25).

A specific chromosome marker has been established on chromosome 3. It was suggested that the genetic factor is located in 3q25 (26). An analysis of spontaneous aberration and chromosome breakages induced by X-rays and folic acid deficiency has revealed that in BEN patients 3q25 band was most frequently involved in the aberrations (27). Three of the additional five bands with increased frequencies of lesions in BEN patients were found to contain oncogenes: 1q36-c src, 3p25-raf-1, and 6q23-myb. The frequent association of BEN and cancer could be explained by the chromosomal hypothesis of oncogenesis. Certain BEN relatives carry chromosomal anomalies that have already described in BEN patients, and it is proposed that they are at high risk for developing the disease (28). Epidemiological data of patients and their healthy relatives are lacking, however, the follow-up studies of healthy relatives could answer the hypothesis that a genetic mechanism might be involved in the development of the disease even in the absence of the exposure to a BEN environment.

Evidence for an inherited metabolic susceptibility to BEN has been obtained by Ritchie et al., using a drug debrisoquine as a probe of variable metabolism (29). The group of BEN patients contained a greater proportion of subjects with enhanced oxidative ability compared to the control group. This is consistent with the view that some individuals, because of their genetically determined metabolic status may be more likely to develop BEN and UTT due to their abilities to activate a chemical present in their environment.

Preliminary results of Pavlović et al. indicate that lecithin-cholesterol-acyl-transferase (LCAT) partial deficiency may play a part in the pathogenesis of BEN-LCAT deficiency is a genetic disease (30). Renal damage in LCAT deficiency is characterized by renal tubular abnormalities. These findings are an argument for the genetic predisposition in BEN.

The erythrocyte  $\delta$ -aminolevulinatase dehydratase (ALA-D) activity was found low in BEN patients and in 32 percent of their healthy family members (31). Lead, a known inhibitor of ALA-D was considered, however, the blood lead levels in BEN patients were well within the accepted normal range, confirming that lead is not involved in the pathogenesis of BEN. It was speculated that genetic as well as environmental factors might explain this observation.

On the other hand evidence is presented that environmental rather than genetic factors play a decisive role in the etiopathogenesis of BEN. Two genetically different populations, natives and immigrants from the Ukraine who settled in the endemic regions near Slavonski Brod, Croatia, have been demonstrated to develop BEN (32).

### Urothelial cancer

The increased frequency of urinary tract tumors (UTT) in the population of endemic villages was described in the first reports on BEN, both in Bulgaria and Yugoslavia (5,33,34). A geographic correlation between UTT and BEN was established in both Yugoslavia and Bulgaria (35,36).

Sporadic cases of the urinary bladder tumours in patients with BEN have been previously described. In Serbia urinary bladder tumors were found equally frequent in endemic and nonendemic regions until 1960. In the last ten years they are becoming increasingly more frequent in advanced stages of BEN, especially with longer survival of patients on maintenance hemodialysis. A recent survey of UTT in the South Morava River basin and its tributaries where BEN is endemic revealed increased frequency not only of tumors of the renal pelvis and ureter but also of urinary bladder tumors (37). Upper tract renal pelvis and ureter urothelial tumors were 57 and 61.8 times more frequent in endemic population than in control rural and city population free of BEN. The frequency of urinary bladder tumors in endemic settlements was also increased compared with the nonendemic villages and large cities, up to 11.9 and 8.5 times, respectively. Familial clustering was also noted. The changing pattern of urothelial tumors in BEN is similar to that seen in analgesic nephropathy, another tubulointerstitial kidney disease associated with urothelial cancer. The early reports pointed out an increased incidence of upper tract urothelial tumors in analgesic nephropathy (38). During the 1953 to 1966 period urinary bladder tumors were equally frequent among abusers and nonabusers, however during the period 1967 to 1977, the overall incidence of urinary bladder tumors increased 7.5 times, and these tumours were 5.8 times more frequent in abusers than in nonabusers (39). An explanation for the recently increased incidence of the urinary bladder tumours was a longer induction time for their emergence. The induction time for tumours of the renal

pelvis was found about 20 years, and about 27 years for tumours of the urinary bladder.

The strong association of BEN and UTT supports the speculation of a common etiology for both nephropathogenic and cancerogenic processes.

### Pathology of BEN

Early autopsy studies performed on BEN patients dying of the end-stage renal failure have revealed shrunken smooth surface kidneys with severe superficial cortex atrophy and sclerosis (40,41). Detailed morphological studies of kidney biopsies in different stages of BEN have permitted to define the initial lesion, target nephron structures and evolution of the kidney damage (42-45). However, not only the etiology of BEN, but also the pathomorphogenesis remained unanswered.

Renal biopsy examinations in the early stages of disease have disclosed changes in proximal tubules. Focal tubular atrophy has been accompanied by interstitial sclerosis. In cases with less intensive involvement, scattered sclerosed areas were usually observed in the superficial cortex. With more extensive involvement, the larger superficial sclerosed areas became confluent and multifocal extending into the deeper cortex. The renal medulla was never significantly involved in the sclerosing process. Immunohisto-chemical localization of laminin, vimentin and cytokeratin 18 in renal lesions of BEN has revealed early changes and major target structures in the disease (46,47). In the normal kidney the interstitium was negative for laminin. In the early stages of BEN a marker overexpression of laminin in renal interstitial capillaries was observed with a moderately increased expression in tubules (46). Later stages were characterized by the intensive expression of laminin in atrophic tubules, much more in proximal than in distal ones. The pattern of laminin staining in corresponded to focal and segmental glomerulosclerosis present in the advanced stages of BEN.

In the normal adult kidney cytokeratin 18 but not vimentin staining was demonstrated in various parts of renal tubules. In BEN cytokeratin was found overexpressed in tubular epithelium, most intense on atrophic proximal tubules (47). Proximal tubular coexpression of vimentin was found corresponding to the degree of proximal tubular damage. Some peritubular blood vessels were also vimentin positive. Very intense vimentin staining was found in the areas of the marked interstitial sclerosis. The coexpression of vimentin with cytokeratin 18 in tubular epithelium found in BEN was described also during development and in damaged kidney. It is a further evidence on the tubulointerstitial lesion in the early stages of BEN.

Renal morphological changes in different phases of BEN were found nonspecific. The predominant pathology of BEN is that of a chronic multifocal interstitial

nephropathy. The findings are nonspecific and resemble those associated with aging (44).

The distribution of interstitial pathology, found more commonly in the superficial cortex, is similar to that seen secondary to vascular involvement. Renal vascular changes were seen in all biopsies and were mostly multifocal than diffuse (42,44). All these vascular changes were found to be only slightly more frequent in patients with low labile hypertension (20%) than in those who were normotensive (80%).

Histological changes in BEN share similarities with renal injuries caused by toxic substances (lead, cadmium, lithium), low molecular proteins, cyclosporine as well as chronic radiation nephropathy. It was speculated that an unidentified factor in the BEN areas may cause earlier occurrence and significantly more rapid progression of aging process.

Immunohistological investigations have revealed moderate mesangial deposition of C3 and IgM in about one third of biopsies, deposits of C3 along the tubular basement membranes in rare cases, and deposits of C3 in small extraglomerular vessels of most biopsies (42,48). Serum complement components and cryoglobulins were in the limits of normal (49,50). Serum immunoglobulins were found in the normal range. Circulating antitubular basement membrane antibodies have not been demonstrated in the sera of BEN patients (51). According to these results, humoral immune mechanisms would not appear to play a pathogenic role in BEN.

It is known that all tubulointerstitial kidney diseases are immunologically mediated. Morphological studies have described rare interstitial mononuclear cell infiltrates (42). In a recent study Ferluga et al. have found that histopathology of BEN is predominantly tubulointerstitial sclerosis without infiltrates. Interstitial inflammatory cell infiltration was found to be present in 38% BEN patients (44). Mononuclear cells predominated and, most often, were the only cells. The interstitial cell infiltrates were never diffuse but always focal and of various extents, and were limited almost exclusively to the renal cortical areas. In 14 percent mixed cell infiltration included some plasma cells and granulocytes.

The role of cell-mediated immunity in the pathogenesis has been studied, however, the results are inconclusive and further studies are needed (52,53).

### Future research of BEN

The etiology remains the major problem for research in BEN. Besides genetic predisposition only a few described environmental factors should be considered. The water-soluble polycyclic hydrocarbons and aromatic amines from weathered coal deposits nearby endemic settlements seems to play a role similar to the acetaminophen reactive metabolites in analgesic nephropathy. Many of these compounds are carcinogenic and could also cause urothelial cancer. The similarity of

renal morphological changes and clinical feature of Chinese herbs nephropathy and BEN has raised the possibility of a common etiologic agent, aristolochic acid. Urothelial malignancy is a common feature of both

nephropathies. A possible detection of DNA adducts formed by aristolochic acid in renal tissue of patients with BEN could reveal its etiologic role.

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## BALKANSKA ENDEMSKA NEFROPATIJA RAZMATARNJE POSLE ČETRDESET GODINA

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*Kratak sadržaj. Balkanska endemska nefropatija (BEN) opisana je 1957. godine, a ovaj pregled daje dostignuća četrdesetogodišnjih istraživanja. Etiologija je najvažniji nerešeni problem u BEN, uprkos brojnim ispitivanjima moguće uloge genetskih faktora, faktora sredine i imunih mehanizama. Izneto je dovoljno dokaza da je BEN izazvana faktorima sredine. Pokazano je neprekidno, ciklično delovanje faktora sredine u endemskim naseljima na bubrege, posebno one iz endemskih porodica. Ispiranje mladih ugljena (lignita) u okolini endemskih naselja proizvodi u vodi rastvorljive aromatične ugljovodonike i aromatične amine, slične metaboličkim produktima acetaminofena, koji imaju ulogu u nastanku analgezične nefropatije. Mnogi od ovih produkata su kancerogeni i mogu dovesti do raka urotelijuma. Sličnost morfoloije i kliničke slike BEN i Nefropatije izazvane kineskim travama, istakla je moguću etiološku ulogu aristolohične kiseline. Genetske studije su dale osnova za genetsku predispoziciju za BEN.*

*Morfologija bubrege u ranoj fazi BEN je posebna i vrlo slična starenju, sa izraženim renalnim vaskularnim promenama. Histopatološki predominira tubulointersticijska skleroza bez ili sa retkim infiltratima. Izgleda da humoralni imuni mehanizmi ne igraju ulogu u BEN.*

*U bolesnika sa BEN i stanovnika endemskih naselja nadjena je povećana učestalost tumora pijeluma i uretera. Skoro je opisana i povećana učestalost tumora bešike. Geografska korelacija između BEN i tumora urinarnog trakta sugeriše da ove bolesti mogu da imaju zajedničku etiologiju.*

*Ključne reči: Balkanska endemska nefropatija, rak urotelijuma, etiologija, prevencija*

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