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Balkan endemic nephropathy: a still unsolved puzzle

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Abstract

Balkan endemic nephropathy (BEN) is a chronic tubulointerstitial renal disease, occurring in certain regions in 5 countries of the Balkan peninsula. Its etiology is largely unknown, though several hypotheses have been formulated and are discussed in this review. In several cases, etiological hypotheses (e.g., viral, ochratoxin or trace element involvement) are verified only in local endemic areas and can not be confirmed when tested elsewhere. Only certain families in the endemic areas are affected. An exposure of at least 20 years to the unknown factors in the endemic areas seems to be mandatory for the development of the disease, but a genetic predisposition to this disease also seems to be mandatory. Prominent clinical features are severely shrunken kidneys, a more severe anemia relative to the level of renal function, and a slow progression to end-stage renal failure. An international approach to solving the etiological and pathogenetic enigma of BEN is needed in the coming years. It is also time to reevaluate other chronic, slowly progressive tubulointerstitial nephropathies diagnosed elsewhere in the world and to search for possible etiological similarities with BEN.

Key words: *Balkan endemic nephropathy, Chronic tubulointerstitial nephropathy, End-stage renal disease, Etiology, Pathogenesis*

Introduction

Balkan endemic nephropathy (BEN) is a slowly progressive chronic tubulointerstitial kidney disease, generating invariably end-stage renal disease (ESRD). It was first described in the late 1950s by Danilović et al in Serbia (1), Tanchev and Dorossiev in Bulgaria (2), and in the early 1960s by Foarta and Negoescu in Romania (3). Though many research programs have been carried out in the last 50 years in the affected countries with or without international involvement, BEN still remains a very controversial disease.

Epidemiology data

BEN is spread over a surface of approximately 500 km^2 comprising the area around the Danube Iron Gate, in settlements along the Danube River and its tributaries (Fig. 1). Currently, BEN has been reported in more than 40 villages in southwestern Romania, in more than 41 villages from the Vratsa and Mikhaylovgrad districts in Bulgaria and in numerous settlements from countries in the former Yugoslavia: Serbia with 73 villages affected, Bosnia with 54 and Croatia with 14 (4). The prevalence of the disease is slightly higher in women than in men. Characteristic and unique to BEN epidemiology is that there are some villages in the endemic regions that are not affected, being separated from the affected areas by only a few kilometers. Moreover, not all households inside the same village are involved: there are BEN-affected families living close to families without any renal disease. Most of the BEN

Fig. 1 - Areas of prevalent Balkan endemic nephropathy.

patients are working as farmers. BEN may also develop in emigrants from an endemic area, if they are descendants from BEN-affected families, even if they have left the region during early childhood and settled down hundreds of kilometers away (5). Furthermore, BEN may appear in immigrants moving into BEN-affected regions. Nevertheless, the development of BEN seems related to the total time (≥20 years) lived in the endemic area (6).

The prevalence, incidence and mortality of BEN differ from one endemic area to another; in Bulgaria the prevalence in the endemic areas varies between 6/1,000 to 12.3/1,000 inhabitants, and the incidence between 0.3/1,000 and 0.7/1,000 person-years (7). In Serbia (Kolubara region) the prevalence varies between 6.4% and 8.9% (8), with BEN representing 11% of all reported causes of ESRD (9). The incidence of deaths was stable over the last few decades, exceeding 3/1,000 person-years in the most heavily affected endemic villages (10). In Romania, the prevalence of BEN in affected villages varies widely between 0.5% and 10% of the population in the endemic areas (3). In recent years, some reports have suggested a decreasing trend for occurrence of BEN (11). However, when evaluating BEN epidemiology in the last 15 years, one must take into account (besides differences in reporting modalities) that war and profound economic and political changes have swept over the Balkans. These facts led to a significant disruption to, and changes in, the medical system and massive demographic changes (emigration); therefore, recent epidemiological data must be interpreted with caution.

Clinical findings and diagnosis in BEN

There are no pathognomonic clinical findings, and there is no specific biological marker for BEN. The disease is a slowly progressive tubulointerstitial nephropathy with first clinical manifestations occurring between 30 to 50 years of age. BEN has not been described in patients aged below 18 years. Most of the cases are diagnosed very late, when signs and symptoms of advanced chronic kidney disease (CKD) or CKD-associated complications have ensued. Early diagnosis in BEN is possible only when affected families from endemic regions are actively investigated or during a planned survey of an endemic area. Severe normocytic, normochromic and nonregenerative anemia is often one of the first clinical features of BEN. The severity of anemia increases further with the impairment of renal function. The serum erythropoietin level is inappropriately low as for the degree of anemia. Mild hypertension may occasionally be detected during an early stage, as well as in the advanced stages of BEN. Urinary sediment has no specific features. Minor and intermittent proteinuria (<1 g/24 hours) has been detected in BEN patients mainly in the later stages. Low-molecular-weight (tubular) proteinuria (β2-microglobulin, lysozyme), as a marker for early tubular damage, is present in BEN patients, as well as in some of the healthy relatives, and is thus a valuable tool in the epidemiological surveys (6, 12, 13). Other signs of proximal tubular damage such as acidification defects, altered ammonia and uric acid excretion and salt loss were also reported (4), in addition to the other nonspecific findings such as polyuria, nocturia, decreased concentrating capacity and high urinary sodium excretion. However, all these abnormalities may occur in any renal disease characterized by tubular dysfunction (12).

In BEN patients, all imaging investigations (ultrasound, intravenous urography, computed tomography and magnetic resonance imaging) reveal common findings: markedly reduced kidney size with a smooth outline (14). It seems that the reduction in kidney size precedes a significant decline in glomerular filtration rate, in contrast to other chronic nephropathies (15). Under these circumstances, the clinical diagnosis of BEN is difficult and is still based on the criteria proposed by Danilović in 1981 (16) (Tab. I). Recently reported multiple kidney function disorders (increased α1-microglobulinuria, glucosuria and decreased tubular phosphate reabsorption) not included in the existing criteria, confirmed that Danilović's criteria are rather appropriate for diagnosis in patients with advanced renal failure (17). Indeed, these criteria supple-

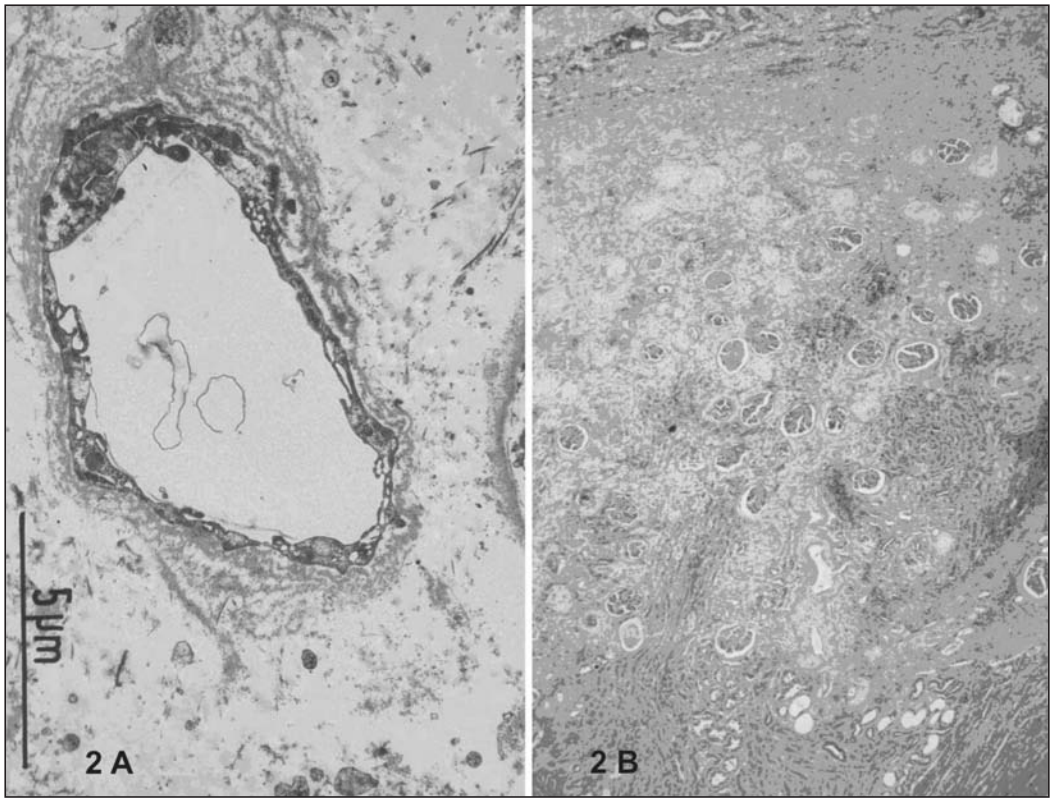

Fig. 2 - A) Electron micrograph shows peritubular capillary sclerosis expressed by basement membrane thickening and splitting in the kidney of a patient with early Balkan endemic nephropathy (magnification × 40). B) Electron micrograph shows widespread sclerosing atrophy particularly prominent in the outer cortex of the kidney in end-stage Balkan endemic nephropathy (magnification × 20; hematoxylin and eosin staining).

mented with the epidemiological data should be revisited, to allow the diagnosis of BEN before the overt (late) clinical manifestations of the disease. In addition, BEN family members with proteinuria should be considered as patients in the early phase of the disease, and this group should be defined as a population at risk for overt BEN development. Finally, a high prevalence of urothelial tumors in BEN patients appears to be a common feature in all endemic areas (3, 6, 12), with a 11.2-fold higher incidence in some of the BEN sites as compared with the nonendemic areas. It seems that urothelial tumors do not histologically differ from those encountered in nonendemic areas (18). Most of the authors suggest a common etiology for BEN and the urothelial tumors.

Pathology of BEN

Histopathology of BEN is characterized by a progressive atrophy and sclerosis involving all structures of the nephron, particularly the interstitium. BEN shares histopathological similarities with chronic toxic tubulointerstitial kidney diseases. In early stages there is multifocal sclerosing atrophy in the cortex, more pronounced in the superficial than in the juxtamedullary areas. Interstitial edema and sclerosis without an active inflammation is found, associated with tubular atrophy, peritubular and occasionally glomerular capillary sclerosis, as well as arteriolohyalinosis (Fig. 2A) (19). In the advanced stages, sclerosing atrophy is widespread, being particularly severe in the outer cortex (Fig. 2B), with consequently smooth-surfaced extremely

TABLE I
CRITERIA FOR THE DIAGNOSIS OF BALKAN ENDEMIC NEPHROPATHY

1. Persons from endemic villages
2. Positive familial history for BEN
3. Mild proteinuria
4. Low specific gravity of the urine
5. Anemia
6. Azotemia (urea >50 mg/dL, serum creatinine >1.5 mg/dL)
7. Symmetrically shrunken kidneys with smooth outline

Note: A positive diagnosis includes the presence of at least 5 criteria (the first 2 are mandatory). Data from Danilović et al, 1981 (16), adapted.

small end-stage kidneys. In the outer cortex, the glomeruli are globally sclerotic, and atrophic tubules vanish, whereas in the inner cortex, they remain relatively preserved until the end-stage disease. Čukuranovič et al performed a quantitative analysis of the renal changes by stereological methods (20); the initial stages of BEN are characterized by a marked increase in the cortical interstitial volume and a concomitant reduction of the glomerular volume. In the later stages, the cortical interstitial volume continues to increase and the glomerular volume further decreases; these findings are associated with a decrease in the volume density of the tubular epithelium and a reduction in the number of interstitial capillaries (20). More detailed ultrastructural analyses revealed a marked overexpression of laminin in the interstitial capillaries and a moderate overexpression in the tubules, as well as a coexpression of vimentin and cytokeratin in the tubular epithelial cells, suggesting that vascular and proximal tubular injuries are the primary events in the initiation of the disease (21).

A SHORT REVIEW OF VARIOUS ETIOLOGICAL HYPOTHESES

After 50 years from the first report and in spite of considerable research efforts made by local and international researchers, the etiology of BEN remains an enigma. Viral infections, environmental toxins and genetic predisposition are the main potential culprits subjected to investigation. The *viral* etiology hypothesis, though very attractive, is supported by scarce data. This hypothesis was raised in the 1970s by Apostolov and Spaic, and Georgescu et al (22, 23), and by Stoian et al in 1983 (24). Later, in 1999, Uzelac-Keserovic and colleagues suggested that the 28.4-nm, nonenveloped virus particles found in the kidney cells of some BEN patients could be coronaviruses (25); however, this finding was not confirmed in a subsequent study by Riquelme et al (26). Recently, it has been found that BEN patients in Bulgaria presented with elevated urinary levels of neopterin, a marker for activated Th1 immune response, virus infections (CMV, HIV, HVA and HVB) and malignancies (27). All of these results are not yet confirmed by data from the other BEN-affected regions.

Many organic and inorganic toxins from food and water have been investigated in relation to BEN, with contradictory results. An excess of certain *trace elements* (cadmium, lead, silica, manganese, copper and selenium) has been related to BEN. In the first description of the disease, Danilović et al suggested that the nephropathy might be caused by lead poisoning (1). Subsequent clinical and epidemiological data could not confirm the lead intoxication theory (28). Selenium deficiency–induced glutathione peroxidase deficiency has been also investigated in BEN patients. Though widespread selenium deficiency has been demonstrated in certain BEN-affected regions, similar to other areas in the world, no direct link between the kidney disease and selenium deficiency could be demonstrated (29). Exposure to the potential toxin seems to have a seasonal variation and is more important during autumn, not supporting an important role for the permanent exposure to trace elements (30).

Mycotoxin-induced poisoning (by ochratoxin A [OTA] and fumonisins) as a cause of BEN is another very attractive hypothesis, since it fits most of the epidemiological features of the disease. The OTA content of food is increased in many of the BEN endemic areas so that OTA intake is higher than in most EU countries, and close to the upper limits accepted by several food-safety organizations (31). OTA is a toxic product synthesized by *Aspergillus* and *Penicillium* species with nephrotoxic, carcinogenic, teratogenic and immunotoxic effects. OTA develops its toxic effect by induction of apoptosis, impairment of mitochondrial respiration and/or the disruption of the cytoskeleton, or by generation of DNA adducts (31). An experimental porcine nephropathy (32) and renal parenchymal carcinoma in mice were described in conjunction with OTA (28). However, experimental toxic doses were significantly higher than those found in severely BEN-affected areas. Intestinal OTA toxicity and a chronic idiopathic interstitial nephropathy have been related to the elevated OTA levels in Tunisia (33), but immunoaffinity-HPLC investigations did not confirm these data (34). Currently, there is no direct evidence for OTA-induced nephropathy in humans (28). Fumonisins are mycotoxins produced by *Fusarium moniliforme*, inhibiting ceramide synthase, the enzyme of de novo synthesis of sphingolipids. Fumonisin toxicity has been linked to the development of BEN in Croatia (34). The data are not yet confirmed in other BEN-affected areas. The possible role of phytotoxins in the etiology of BEN was raised in the early 1970s (35). The seeds of *Aristolochia clematitis* contain a potent phytotoxin (aristolochic acid I and II [AA]) with nephrotoxic and carcinogenic effects in animal and humans. AA is a genotoxic mutagen forming DNA adducts after metabolic activation, involved in carcinogenesis and generating extensive interstitial renal fibrosis by an unknown mechanism (36). In the early 1990s, aristolochic acid nephropathy (AAN, also known as

Chinese herb nephropathy) has been described after accidental AA poisoning (37). The contamination of wheat grain with *A. clematitis* during harvesting has been demonstrated in Croatia; the flour used to bake bread was also contaminated with AA (38). AAN is a rapidly progressive interstitial nephropathy characterized by early, severe anemia, mild tubular proteinuria and initially normal arterial blood pressure in half of the patients. Renal histology shows many similarities to BEN, extensive cortical interstitial fibrosis associated with tubular atrophy and glomerular sclerosis, decreasing in intensity from the outer to the inner cortex. Urothelial malignancy of the upper urinary tract is highly prevalent in AAN and BEN (39). Due to these similar morphological and clinical findings, the hypothesis of a common etiology has been raised (37). However, endemic nephropathy was not described elsewhere, other than in certain areas from the mentioned countries, though *Aristolochia* is a source of contamination in many parts of the world, including nonendemic areas from BEN-affected countries.

Poisoning of the drinking water with *water-soluble hydrocarbons* from Pliocene-epoch lignites is another attractive etiological theory. The US Geological Survey and researchers from the affected countries have demonstrated that all endemic areas with exception of 1 in Serbia lie over Pliocene coal deposits (40). These lignites still contain water-soluble complex organic compounds, which are diluted into the drinking water. Certain compounds – polar polycyclic aromatic hydrocarbons and aromatic amines – have been identified in the drinking water from the endemic areas. These compounds are known to be carcinogenic, in particular causing urothelial cancer (41, 42). However, Pliocene lignite deposits are spread over the world (including Europe, Australia, China and the United States), and to our knowledge, no endemic nephropathy has been described in those places.

Since the precise substance(s) involved in the genesis of BEN have not yet been identified despite all the extensive research, a simple question emerges: why are some hypothetical substances toxic to certain subjects and induce BEN, while causing no harm to other people from the same area? A plausible hypothesis suggests that BEN is generated by the action of environmental factors in *genetically predisposed individuals*. This is supported by some striking aspects of the epidemiology of BEN: in the endemic area only certain families are affected; the "healthy" offspring of BEN patients have shorter kidney lengths (13); offspring from BEN patients excrete significantly more albumin and β_2-microglobulin than subjects from nonaffected families even when living in the same settlements (13, 28). Furthermore, Toncheva et al reported that BEN patients have a higher rate of spontaneous and radiation-induced chromosome aberrations, as compared with the controls (43). A specific chromosome arm linked to BEN (3q) has been described (44). It was hypothesized that certain chromosome aberrations may involve oncogenes, which could explain the frequent association of BEN and urothelial cancer. In the 1990s the predisposition for BEN was related to genetically determined deficiencies in enzyme activity, involving lecithin:cholesterol acyltransferase (LCAT) (45), erythrocyte δ-aminolevulinate dehydratase (ALA-D) (46) and cytochrome P450 2D6 (CYP2D6) (47). Decreased activity of these enzymes has been proposed for the assessment of the risk to develop BEN (45). The Atanasova et al and Toncheva et al investigated the role of genetic polymorphisms of several enzymes from a detoxification system, in Bulgarian BEN patients (48-50). It seems that cytochrome P450 3A5*1 (CYP3A5*1) allele carriers are at higher risk of BEN. A similar risk has been described for BEN patients with the glutathione S transferase M1 (GSTM1) wild-type allele (51). Research from Bulgaria showed also that persons with particular variants of the renal transporter proteins (P-gp) might be at lower risk to develop BEN (52). However, these findings have yet been confirmed in other endemic areas. Finally, there are some suggestions that BEN might be a disorder of renal *embryogenesis,* characterized by a deficit of nephron number, induced by environmental factors with an impact on embryogenesis. This theory is supported by the increased occurrence of renal dysplasia-hypoplasia in BEN patients (compared with other nephropathies), the high incidence of renal pelvic and renal artery anatomic abnormalities, the finding of primitive glomeruli and obstructed tubules on kidney biopsy, and the frequent occurrence of a generalized proximal tubular dysfunction similar to adult Fanconi syndrome (53).

Prevention and treatment

Since the etiology is not yet known, there are no effective strategies for prevention of BEN. Common sense measures such as using a water supply from distant sources and migration of affected families outside the endemic area should be encouraged. The treatment of BEN is mainly the same as the treatment of any chronic kidney disease with unknown etiology. It includes general measures and dialysis for end-stage renal disease. As the risk of developing

urothelial tumors increases with longer survival of the BEN patient (including the end-stage renal patient), a surveillance program for neoplasia of the urinary tract is mandatory. Kidney transplants have been performed in several patients, and recurrence of endemic nephropathy in grafted kidneys has not been documented (12).

Conclusions and final comments

Balkan endemic nephropathy is a chronic tubulointerstitial renal disease, occurring in certain regions of the 5 countries of the Balkan peninsula. Etiological factors leading to BEN are largely unknown, though several hypotheses have been formulated. Only certain families in the endemic areas are affected. An exposure of approximately 20 years to the unknown factors in the endemic area seems to be required for development of the disease, but a genetic predisposition to this disease is plausible. Prominent clinical features are severely shrunken kidneys, a more severe anemia relative to the level of renal function (and in comparison with other renal diseases) and slow progression to ESRD. After 50 years since identification of Balkan endemic nephropathy, we are still fighting with an unsolved puzzle: its etiology. This puzzle is becoming more and more complicated along with the evolving new research hypotheses, which have not been accurately tested and confirmed yet. In several cases, etiological hypotheses have been verified only in local endemic areas, and they can not be confirmed when tested elsewhere. It becomes even more apparent that if we want to resolve the puzzle, an international, coordinated approach is needed. Finally, it is possible that even the concept of "Balkan nephropathy" limits our way of thinking, as well as our diagnostic approach. We consider that it is also time to reevaluate, with an open mind and a fresh perspective, other chronic, slowly progressive tubulointerstitial nephropathies diagnosed elsewhere in the world and to search for possible etiological similarities with BEN.

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