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Balkan nephropathy

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Introduction

Balkan (or endemic) nephropathy is a chronic tubulointerstitial disease of unknown, presumably exotoxic etiology. It has been shown to exist only in some parts of the southeastern Europe.

While there have been many meetings and papers [1, 2] concerning both cause and treatment of Balkan nephropathy, sociopolitical turmoil, including wars, and economical hardship prevented any meaningful research on the problem during the 1990's. Thus, despite numerous proceedings and a large number of publications on the subject, many features of Balkan nephropathy, its etiology and natural history in particular, remained nearly as mysterious as when described in the mid-fifties.

Meetings organized by international organizations [3-7] had a key role in informing the international scientific community on the disease. A recent source of information is a bilingual (in English and Serbian) monograph published in 2000 [8].

Epidemiological features

Distribution and frequency

Though exclusive geographical restriction of the agent(s) of Balkan nephropathy is not very likely, the disease has been diagnosed only among people living (or those who used to live) in more or less well defined areas of the Balkans. Along with Bulgaria and Romania, three republics of the former Yugoslavia have been affected: Bosnia, Croatia and Serbia, including Kosovo (Figure 1).

As recently summarized [9], the affected territory has a shape of a rhomboid. Its longer diameter spreads over 500 km (from the Vratza municipality in Bulgaria to villages west of Slavonski Brod in Croatia), while its transversal diameter has about 300 km (from endemic foci in eastern Romania to Vitina municipality in Kosovo). The disease affects individuals who live (or used to live) in rural environment. There are spared households even in the most affected areas, leading

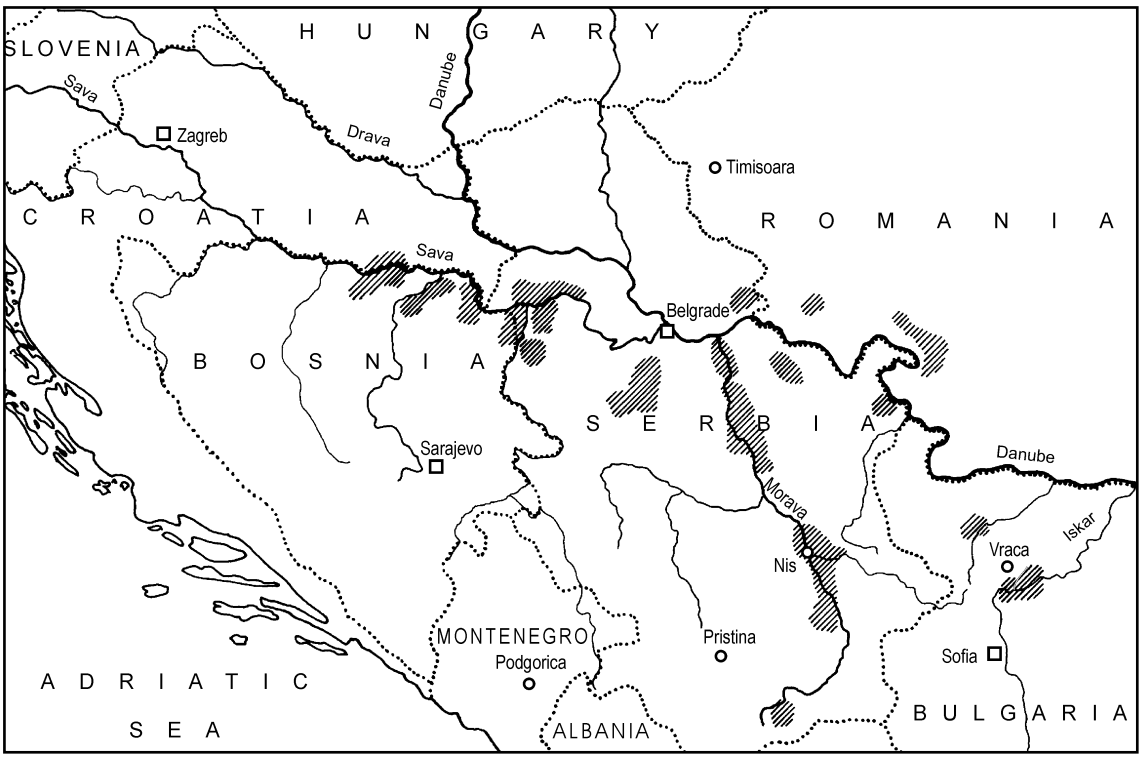

Figure 1. *Medical geography of Balkan nephropathy.*

to frequently cited remarks on mosaic distribution of the disease.

Topography of the terrain differs between endemic regions. All 14 endemic villages in Croatia are located in a single lowland municipality, at an altitude of about 100 m, while Bosnian foci are found up to 130 m. About 90% of all endemic settlements in Serbia are also situated at a low altitude, below 200 m. [10], either in large plains, river valleys or, much more seldom, in hilly regions. There have been no studies of medical geography of Balkan nephropathy in Romania for the last 40 years and endemic localities are yet to be determined [11], but the original findings pointed out to hilly areas, with endemic villages laying at the bottom of valleys eroded by flooding, at an altitude of 200-300 m. The endemic region in Bulgaria was described as mountainous or semi-mountainous, without any relationship between endemicity and altitude. Hydrogeological features [12] and lack of floods differentiate (at least some) Bulgarian foci from other typical endemic regions.

Controversial data on the frequency of Balkan nephropathy were mainly result of methodological shortcomings [9]. A main obstacle was the operational definition of the disease, leading to huge differences in estimated prevalence rates. The highest ever recorded average annual incidence rate was 16.6 per 1000 in Cakonica, Bulgaria. The average cause-specific mortality rate from Balkan nephropathy over 15 years in one of the most affected Serbian foci was 3.3 per 1000 [13].

Demographic data

During initial Balkan nephropathy research, patients were frequently in their thirties [14], and it was widely accepted that azotemia usually affects the age group 30-50 [3]. Later an apparent shift towards the older ages occurred, with most identified patients being above the age of 60 [9]. The diagnosis of clinical forms before the age of 20 was rare and never independently confirmed. Despite occasional statements on laboratory and bioptic abnormalities in the first decade of life among clinically healthy children from endemic areas, no follow up study ever showed that these children developed subsequently kidney disorder.

Both genders are similarly affected, especially considering mortality. As explained in details elsewhere [9], higher prevalence rates among women reported by some authors appears to be a consequence of unreliable diagnostic criteria.

A vast majority of experts believe that a link exist between agricultural activity and exposure to the agent(s) of Balkan nephropathy. There is also near consensus on the absence of ethnic and/or religious differences as a risk of developing the disease. The most convincing data come from Croatia, where the large group of Ukrainians who settled a century ago had the same odds of being affected as the indigenous population. The first generation immigrants developed Balkan nephropathy usually a couple of decades after moving into an endemic region.

Initial studies of affected households showed a low standard of living, poor hygienic level, and insufficient nutrition. However, socio-economic factors, including living conditions and well water quality, did not differ between contiguous affected and non-affected households or between endemic and neighboring non-endemic villages.

Chronological characteristics

The initial description of Balkan nephropathy emanated from Bulgaria [15, 16] and Serbia [17-19]. By 1957, the disease was recognized in Bosnia and Croatia and by 1958 in Romania [20].

On retrospect, it was not a newly emerging condition but rather recognition of an already existing endemic process, a previous epidemic wave seems having occurred in the early forties. Unfortunately, attempts to trace the disease prior to World War 2 are speculative, due to the absence of reliable data and a high frequency of the competing causes of morbidity, notably tuberculosis and malaria.

As for the secular trend, two facts, common to all endemic areas, are crucial in assessing any future dynamics of the disease. These are, an apparent shift of the age distribution of the incidence towards the older age groups, and a much longer natural history of the condition compared to previous data. Consequently, it suggests that the intensity of exposure diminished (if still present at all).

Other epidemiological characteristics

Clustering of cases within a household is one of the most conspicuous features of the disease. It is generally

agreed that the disease affects both blood related and non-blood related family members. The "phenomenon of simultaneous deaths" (dying of parents and their children within a short interval) was also observed.

Between 1/3 and 1/2 of patients with Balkan nephropathy develop urothelial tumors [21]. An exceptionally high frequency of these tumors was also observed in the general population of endemic regions [22]. When initially studied, the attributive risk of developing upper urothelial tumors in inhabitants of endemic foci amounted to several dozen or even to as much as 100-200.

There is no evidence that domestic and/or wild animals in endemic regions develop a similar condition.

Overview of the descriptive epidemiological research

There is general agreement on the following descriptive-epidemiological characteristics of Balkan nephropathy [9]: The disease is known to exist only in some parts of the southeastern Europe, with Central Serbia as the most affected region. Balkan nephropathy does not spread beyond its already defined foci; the disease is distributed mosaically: non-endemic villages exist in the most affected regions, and there are spared families and households in the most affected settlements. Clustering of cases in families and households has been described. Children and adolescents are spared of clinical disease. Incidence is proportional to age, except for the oldest age groups. There are no major sex differences in the cause-specific mortality rates. The excess risk of developing transitional cell urothelial tumors was expressed by two- or even three-digit numbers.

The large majority of researchers support the following statements [9]: autochthonous urban population is spared; rural way of life, i.e., agricultural activity is needed for exposure to the agent(s). Separation from an endemic focus early may prevent the disease, while immigration to an endemic area provides risk of disease development, providing that the exposure was sufficient. Prevalence of the disease has been stable over many years, but now appears to decline in most affected settlements. Incidence rates are shifting towards the older age groups, and the clinical course is much more protracted suggesting a less intensive contact with the agent(s) and, consequently, possible future spontaneous disappearance of Balkan nephropathy.

Etiology

Genetic factors

The most elaborate and, seemingly consistent, hypotheses regarding etiology initially came from proponents of heredity as an explanation of the disease occurrence. These authors assumed that the risk of developing the disease was restricted only to specific, ethnically distinct, population groups, irrespectively of their place of birth and residence history. Wider acceptance of these hypotheses was hampered by the different perception of descriptive epidemiology of Balkan nephropathy by a majority of researchers on the topic.

A specific chromosome marker (3q25) in Balkan nephropathy patients from Bulgaria was identified, and this isolated finding was used to support arguments in favor of a crucial role of genetic factors [24-26]. More recently, the same authors acknowledged that environment is also important [27]. Some aberrations of the X chromosome have been reported, but they resembled changes occurring after exposure to ochratoxin A [28].

Major anomalies of urinary organs allegedly occurred in a high percentage of otherwise healthy children from affected households. However, such a finding has never been replicated.

Genetic epidemiological approach suggest two possibilities, either polygenic type of inheritance with an insufficient expression of the main gene [29], or monofactorial model with a crucial role of a single gene of incomplete penetrance [30]. In both cases, contributing environmental factor is needed.

There is no evidence supporting an immunological mechanism in Balkan nephropathy.

Biological agents and their products

Unspecified viral particles [31], an unidentified cythopathogenic agent, serially propagated slow viruses [32], and an unknown virus associated with foci of natural infection [33] have been mentioned in the context of Balkan nephropathy etiology. Several specific viruses, notably West Nile [34], coronavirus [35], and papova virus [36], were also suggested as a causative agent. A common feature of all these hypotheses was unimpressive supporting evidence and ignorance of

basic epidemiological features of the disease, in particular its absence of spreading [37].

Bacteria received particular attention in initial stages of the Balkan nephropathy research but their possible etiological importance has been unanimously considered as ruled out [2]. Protozoa have never attracted any attention.

Toxic fungal products were until recently the principle and prime potential culprits. Most efforts have concentrated on ochratoxin A, a mycotoxin responsible for porcine (swine) nephropathy [38]. The substance is found in endemic foci but it is also present in neighboring non-endemic areas, and the differences are not statistically significant [39, 40]. Still, the consistent isolating of ochratoxin A in greater frequency and higher concentrations from food and sera samples obtained from endemic, compared to control villages, offered some arguments in favor of this hypothesis.

Association of ochratoxin A with chronic interstitial nephropathy in Tunisia [41] and its relation to renal tumors [42] provides additional support for the idea of the etiological role of this mycotoxin. Other fungal toxins, as zerealenone, citrinin [43] and aflatoxin were also isolated in endemic foci. Experimental models suggested that a combination of mycotoxins, rather than a single one, might be involved in the etiology of Balkan nephropathy [44].

Aristolochic acid and its salts, originated from a weed, *Aristolochia clematitis*, have toxic and carcinogenic effects to the kidneys and urothelium [45], respectively. Ivic [46] postulated that this plant may be a cause of Balkan nephropathy, but failed to provide convincing evidence from field surveys. Evidence that *A. clematitis* played a central role in the etiology of Chinese herb nephropathy [47-49], a condition similar to Balkan nephropathy, initiated a second look at this previously abandoned hypothesis and it gained a lot of weight by recent data on the association between DNA adduct formation derived from AA, mutation pattern and tumour development in BEN [50] (see also chapter 33).

No local practice in terms of the use of teas or folk medicine could have been implicated. No one has ever studied flora of the local wells.

Agents from the inanimate environment

Chronologically, lead poisoning was first offered as an explanation for the occurrence of Balkan nephropathy [17-19]. The idea on lead-contaminated flour led to abandonment of water mills in a part of Central Serbia. This energetic public health action had no impact on the disease frequency.

Effects of non-occupational exposure to cadmium [51], itai-itai disease in particular [52, 53], were occasionally compared with kidney damage seen in Balkan nephropathy patients. In spite of some resembling features, the idea of a common etiology between cadmium nephropathy (including itai-itai disease) and Balkan nephropathy was refuted [52, 54].

Many other metals, including radioactive ones such as uranium [55], were also suggested as possible causative agents of the disease. Results were non-convincing and non-reproducible. Inability to identify a single toxic effect of any metal or metalloid as a cause of Balkan nephropathy led researchers to two alternative approaches. First, deficiency, rather than abundance of such a chemical element was proposed [56], with selenium as the most likely candidate [57]. Second, attention was paid to a combined adverse effect of several elements. Synergism of uranium and some other elements, none of which exceeding maximal allowed levels, was proposed [58]. It was also noted that criteria used in occupational medicine (exposure only during working hours) have been applied to an ecological problem (constant exposure) and that concentrations of lead or cadmium within formally acceptable level, combined with other factors, such as selenium deficiency, might lead to the disease [58]. All these suggestions remained speculative.

As for non-metals, there were attempts to relate Balkan nephropathy to silicon [59-62]. However, when affected and non-affected households were compared, there was even an inverse relationship between the silica content and endemicity. On one occasion, small differences in silica content happened to reach the level of statistical significance but the association was explained as a result of confounding variables [63].

Common hydrogeological characteristics of endemic foci [12] and inverse relationship between altitude of wells and disease frequency in a longitudinal (cohort) study [63], pointed to potable water as a vehicle of the agent(s). However, none of the already mentioned or several dozen other non-organic substances were associated with the disease [64].

Organics in water have been investigated and pro-

vided some interesting data [65]. Except for nitrites [66], chemically unstable substances have not been studied. Wells associated with the disease were reported as situated on alkali soil [67], but the finding was restricted to a single endemic area and never reproduced.

Based on chronological data, it is clear that no pesticides, fertilizers or chemicals introduced during the last few decades may be blamed for the occurrence of Balkan nephropathy. Except for exposure to agricultural activities, no occupation, habit (e.g., smoking, alcohol consumption), or hobby (e.g., hunting, fishing) might have been shown to precede the disease onset.

Overview of the etiological research

Genetic factors may play a role in different individual risk of developing Balkan nephropathy, upper urothelial tumors, both diseases or none of them [68]. However, epidemiological data indicate that one or more external, environmental factors are crucial for the occurrence of both Balkan nephropathy and excessive frequency of these tumors in endemic areas.

Among biological agents and their products, the candidates for etiological agents are mycotoxins and, much more probably, toxic plants, notably *Aristolochia clematitis*. The possible role of viruses is very unlikely, indeed.

As for inanimate environment, there is no chemical element that has been consistently detected in higher concentrations in biological material of Balkan nephropathy patients and/or their environment, as compared to the controls. However, though unlikely, insufficiency of an essential element has not been completely ruled out. Speculations on a combination of vaguely defined environmental factors have never been substantiated by facts.

Pathomorphological Changes

Balkan nephropathy is non-destructive and non-inflammatory tubulointerstitial renal disease [69]. The changes are non-specific and in the chronic, sclerotic phase they may be quite similar to changes observed in other chronic interstitial diseases such as analgesic nephropathy [70], vascular nephrosclerosis [69] cyclosporine-induced nephropathy [71], radiation nephritis [72, 73] and aging [72], intoxication with silicate, cadmium, lead, uranium [74], mycotoxin ochratoxin A [75], Aristolochia clematitis [46], and recently with Chinese herbs [47, 49].

Macroscopic features

Before introduction of hemodialysis in the treatment of chronic renal patients, the kidneys of patients who died of Balkan nephropathy used to be the smallest seen at post mortem examinations, weighing 14.8-80 g each (Figure 2A) the difference between the left and right kidneys being small (5-20 g) [74, 76-78]. Surface of the kidneys is smooth, occasionally wavy but never granulated or roughly nodular. The section shows markedly narrowed cortex, pyramid and Bertin's columns are fairly well preserved, and corticomedular border is well differentiated. Papillary necrosis of the pyramids has not been found.

Small, papillary, usually multiple tumors of the renal pelvis and ureters are also one of the characteristic findings (Figure 2B]. In post-mortem studies tumors were reported in 8-50% of cases [74, 79].

Morphological studies of renal changes in post mortem material

Diffuse fibrosis of cortical interstitium and tubular atrophy may be observed along in the absence of sig-

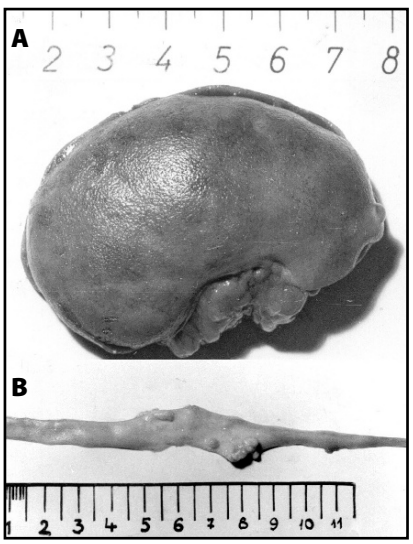

Figure 2. A. *Macroscopic appearance of the right kidney weighing 35 g in a case of BN, surface if smooth, occasionally mildly wrinkled (Autopsy, a man aged 48).*
B*. Multifocal papillary tumor of the right ureter (autopsy).*

nificant cellular interstitial infiltration. In contrast to the cortex, Bertin's columns are less markedly affected. Even in severe tubulointerstitial cortical changes, glomeruli are well preserved, partially collapsed, and subsequently subjected to focal or generalized sclerosis mainly collapsing. Glomeruli in Bertin's column are occasionally compensatorily enlarged. Pyramids are preserved or less markedly affected [74, 76, 79].

Blood vessels, arcuate or interlobular arteries, and arterioles are affected in the form of intimal sclerosis and thickening of lamina elastica interna. In addition, the blood vessels are compressed and torsioned [79].

In cases of tumors of the renal pelvis and ureters morphological signs of pyelonephritis are often found [74].

Optic microscopic, immunofluorescent and electron microscopic studies of renal biopsies

In oligosymptomatic clinical cases, rare disseminated foci of interstitial fibrosis and tubular atrophy with preserved glomeruli are seen. These changes have no special predilection of distribution and are not inflammatory. They tend to be triangular, with the base oriented toward the renal surface [69, 79]. In cases with initial renal failure, the fields of acellular interstitial fibrosis are larger and even diffuse.

The striking atrophic process observed in Balkan nephropathy suggests that apoptosis may play a role in this disease. In this context it is of interest that Savin et al. observed an increased apoptosis to proliferation ratio at the level of the tubuli [80].

The glomeruli are usually affected by generalized [80%] or segmental sclerosis [10%]/ and only in 8% hyalinosis is recorded. Double contour glomerular basement membrane was recorded in 22% of the cases. In 2.7-6% of cases fetal-like glomeruli can be seen in the kidneys, while glomerular hypercellularity was recorded in 4% [72, 79, 81].

The most interesting changes are recognized in pre- and postglomerular blood vessels. In about 50% of cases PAS positive proteins are deposited in vas afferens walls in a focal segmental or circumferent manner in the form of droplets, bands or granules [72, 79, 81].

Interlobular capillaries are filled with thick proteinaceous substances that are also deposited below the capillary endothelium and may even be found free in the interstitium. These changes are described as capillary sclerosis [70]. Although renal vascular changes in Balkan nephropathy have been pointed out as very important, they are not specific and can be encountered in other renal diseases. Ferluga et al. [72] and Sindjić [79] commented on their similarities with cyclosporine induced nephrotoxic changes.

Immunofluorescence revealed irregular and scarce deposits of C3, fibrin and IgM, and occasionally IgA, C1q and C4, mainly on the vascular walls, Bowman's capsule and some sclerotic glomeruli [69, 82, 83].

Electron microscopic findings are either normal or correspond to degenerative and sclerotic changes. While some authors describe virus-like particles [35, 84, 85], others point out that such particles were not found [72, 73].

Despite these findings, some authors described Balkan nephropathy as a form of glomerulonephritis [81, 86]. However, the lack of reliable evidence supporting glomerulonephritis has lead to it being discarded [73, 77] and abandoned even by its advocates [87].

Optic microscopic, immunofluorescent and electron microscopic studies of renal biopsies in children aged 5-15 from affected families in endemic regions failed to detect any Balkan nephropathy related changes [79].

Overview of morphological studies

It is generally agreed that the morphological changes of Balkan nephropathy are not specific and correspond to non-destructive, non-inflammatory kidney disease accompanied by marked changes on the blood vessels in both early and late stages of the disease, interstitial, multifocal fibrous expansion and severe tubular atrophy mainly in the upper cortex [69, 72, 73, 79, 81].

Changes on kidneys arterioles have been described suggesting that the changes in early stage of the disease may be responsible for the development of multifocal, ischemic, vascular nephrosclerosis encountered in chronic stages of the disease [69, 72]. On the other hand, close similarity of Balkan nephropathy with analgesic and cyclosporin-induced nephropathy has been recognized [71, 72, 79]. All this leads to a suggestion that Balkan nephropathy develops following a model of toxic nephropathy, targeting primarily the vascular endothelium where the tubular epithelium is affected either directly or indirectly due to accompanying ischemia.

Clinical features, diagnostics and treatment

Clinical picture and course

Balkan nephropathy is a chronic tubulointerstitial disease with occult, insidious onset, usually progressing slowly with no apparent signs of symptoms. After a long asymptomatic period, the disease is manifested as chronic renal failure. Less commonly blunt lumbar pain or renal colic may develop or, occasionally, dysuric symptoms induced by urinary tract infection. If hematuria exists, urothelial tumor should be suspected. In an advanced case polyuria and nocturia are present due to impaired concentrating ability of the kidneys. The disease is tolerated well and the patients preserve their working ability until advanced stages of renal failure [18, 76, 88, 89].

Objective examination reveals characteristic skin tan of Balkan nephropathy patients: a pale yellow with copperish glow on the cheeks has been recognized since the augural reports on the disease [18, 88]. Besides, xantochromia of the palms and soles is also frequently observed. In the advanced phase of the disease physical examination detects signs of chronic renal failure [19].

Patients with Balkan nephropathy do not suffer from edema, and their blood pressure is usually described as normal [18, 88-90]. Recently, several studies reported a higher prevalence of hypertension even in offspring of Balkan nephropathy families [91, 92, 93].

As Balkan nephropathy is characterized with slow asymptomatic course, most authors identify two main stages of the disease: the first, asymptomatic (latent, subclinical) and second, manifest (symptomatic). The latter is usually subdivided into the stage without renal failure (early, compensated Balkan nephropathy, with no azotemia) and chronic renal failure (decompensated Balkan nephropathy, uremia) [19, 88, 89].

An important feature of Balkan nephropathy is its association with a high incidence of tumors of the renal pelvis and ureters, but not urinary bladder tumors [22, 94, 95]. However, the difference between the incidence of upper urothelial tumors in endemic and non-endemic regions diminished in the last decades. In the sixties and seventies the incidence of these tumors was reported to be several dozen times higher in endemic than in non-endemic regions, while in the last decades this difference almost disappeared [21, 22, 94, 96, 97]. Upper urothelial tumors of patients originating from the region with Balkan nephropathy differ from tumors identified in patients from other regions in their similar incidence in both sexes, bilateral occurrence, and more common association with chronic renal failure [95].

Laboratory findings

Appearance and urine color are unchanged in most patients with Balkan nephropathy. Urine sediment is usually scarce, while microhematuria or leukocyturia are usually associated with the occurrence of tumors or urinary tract infection [88, 89].

Bacteriological studies usually reveal sterile urine, but in 8.3-31.8% significant bacteriuria was confirmed and considered as superimposed urinary tract infection [88, 89].

Proteinuria is a common finding in patients with Balkan nephropathy [18, 88]. It is usually intermittent, less than 1 g per day and it becomes permanent in advanced renal failure [98]. Although proteinuria is one of the criteria for diagnosis of Balkan nephropathy, it has been reported in healthy members of endemic families [30, 98, 99]. Tubular proteinuria is the most common and increased excretion of low-molecular weight proteins such as β_2-microglobulins, lysozyme, ribonuclease, light chains of immunoglobulin, retinol-binding protein has been reported [100-105]. Beside tubular proteinuria, smaller numbers of patients manifest mixed proteinuria, while in patients with renal failure, glomerular proteinuria may be encountered [103, 105].

Anemia has been noted in patients with Balkan nephropathy in early studies [18] and described as normocytic and normochromic or mildly hypochromic [88]. It has been suggested that anemia occurs earlier in the course of the disease progression than is the case in other renal diseases and that it precedes azotemia [88, 106]. However, recent studies have failed to substantiate this claim [98, 107]. Also, there is no evidence that anemia in Balkan nephropathy differs from anemia accompanying other renal diseases in either features [107] or rate of deterioration in the progression of renal failure [108]. Nevertheless, anemia in Balkan nephropathy patients treated with hemodialysis is more severe than in patients with other renal diseases [108].

The leukocyte count in the peripheral blood of patients with Balkan nephropathy is normal and without

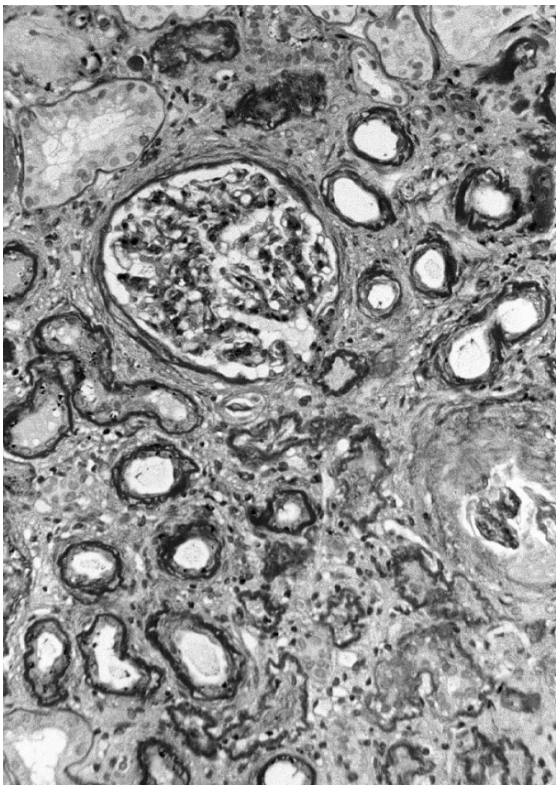

Figure 3. *Interstitial fibrosis and tubular atrophy; glomerulus with mild mesangial hypercellularity and another with incomplete hyalinosis. PAS, x120.*

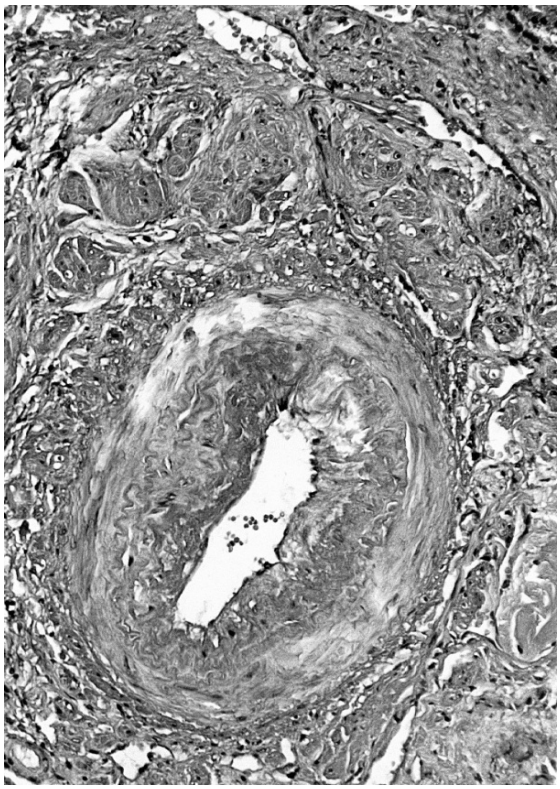

Figure 4. *Interlobar artery showing intimal fibrosis. PAS, x240.*

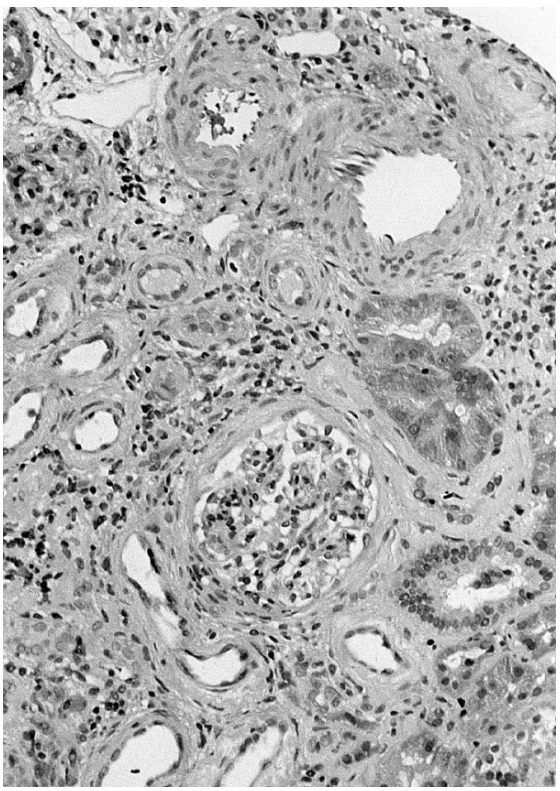

Figure 5. *Reduced number of tubules; fibrotic interstitium; few infiltrating cells. Masson's trichrome, x120.*

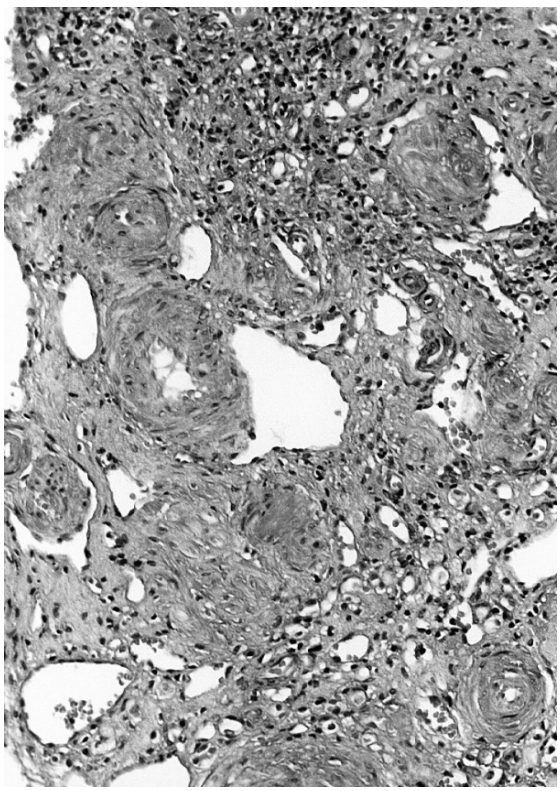

Figure 6. *Extensive interstitial scarring associated with severe arterio and arteriolosclerosis. PAS, x120.*

pathological changes in the differential count and bone marrow [19, 88].

Investigation of renal function in patients with endemic nephropathy has revealed tubular dysfunctions in the earliest stage of the disease: renal glycosuria, increased uric acid and amino acid excretion [101], as well as increased excretion of low molecular weight proteins [104]. Significantly higher activity of cellular enzymes in the urine and increased urinary excretion of Tamm-Horsfall protein was described in patients with Balkan nephropathy, as well as in healthy members of endemic families [109]. Findings of a distal tubular disorders (impaired urinary acidification, impaired urine concentrating ability) were described in earlier studies [88, 89] but could not be confirmed in studies conducted in larger groups of patients with normal or mildly impaired glomerular filtration rate [98, 110]. The occurrence of certain disorders of the tubular function recorded in the course of chronic renal failure (increased natriuria, phosphaturia) can be considered as the result of kidney adaptation to the lost nephron mass, instead of Balkan nephropathy properties [110].

The immunological studies have failed to indicate that immune disorders participate in the pathogenesis of Balkan nephropathy, with some of detected changes having been attributed to advanced renal failure [111].

Imaging methods

Different methods of kidney imaging have shown that Balkan nephropathy patients with chronic renal failure have symmetrically shrunken kidneys with smooth surface and no calcifications [90]. The time at which the shrinking occurs remains to be determined. While some authors suggest that the size of the kidneys remains normal in patients in the latent phase of the disease and with normal renal function, others report cases of shrunken kidneys in patients in an early phase with normal glomerular filtration rate, and it was even proposed that the disease was characterized with primarily small kidneys [98, 110, 112]. As ultrasound became a standard imaging method in the evaluation of kidney dimensions, several recent studies that used this method showed diminished kidney length and cortex width in members of Balkan nephropathy families with normal kidney function [113, 114]. Besides, significantly shorter kidney length, as well as higher protein, albumin and b2-microglobulin excretion was found among offspring with a maternal history of Balkan endemic nephropathy (BEN), not a paternal one [113] .

Excretory urography does not reveal changes in the pyelocaliceal system, except in cases with secondary infection or urothelial tumors.

Radionuclide methods have shown that renal plasma flow impairment is the first sign of the early phase. Glomerular and tubular functions correspond to the severity of the disease.

Diagnosis

The most commonly used criteria for the diagnosis of Balkan nephropathy are still those proposed by Danilović [106]. They include: 1) farmers living in the endemic villages, (2) familial history positive for Balkan nephropathy, (3) mild proteinuria, (4) low specific gravity of the urine, (5) anemia, (6) retention of nitrogen compounds in the blood (urea > 50 mg/dl, creatinine > 1.5 mg/dl) and (7) symmetrically shrunken kidneys. Using these criteria, Danilović suggested classification of patients in field studies into the following groups:

1. *potential,* a group with intermittent proteinuria, those that fulfill at least the first three criteria,
2. *suspected patients*, that in addition to the first three fulfill at least one of the remaining three criteria,
3. *affected patients*, that fulfill at least 5 out of 6 criteria,
4. *decompensated* patients that fulfill at least 5 out of 6 criteria and have urea values >150 mg% and manifested signs of uremia.

Analysis of these criteria leads to the conclusion that they enable detection only of patients with overt disease, and the criteria are not sufficiently specific to enable a reliable diagnosis. Therefore, numerous studies have been focused on developing sufficiently sensitive and specific criteria to enable diagnosis in the early phase. Although markers of tubular disorders, particularly tubular proteinuria, may be used as sufficiently specific diagnostic criteria, so far not a single clinical or laboratory finding is considered pathognomonic for Balkan nephropathy when differentiate it from other, specially, tubulointerstitial diseases.

The diagnosis of Balkan nephropathy is now established according to the first two criteria (residence in

endemic village and positive family history) suggested by Danilović [106], presence of tubular proteinuria and ruling out other renal diseases.

Histopathological analysis makes the diagnosis of Balkan nephropathy significantly easier [72, 79], and it is considered indispensable in classifying the following groups of patients with urinary abnormalities suggestive of endemic nephropathy:

1. Patients from families that were not previously been affected with endemic nephropathy, but live in an endemic village,
2. In cases of nephropathy of unknown etiology in villages close to endemic foci,
3. In immigrants to endemic regions and in emigrants from these regions [111].

Differential diagnosis of Balkan nephropathy should include all chronic, slowly progressive renal diseases, primarily chronic tubulointerstitial diseases. Although no specific indicators of Balkan nephropathy have been recognized, epidemiological data, familial history as well as clinical characteristics of the disease enable differential diagnosis. Thus, shrunken kidneys with smooth surface are characteristic of Balkan nephropathy and they differentiate it from analgesic nephropathy, pyelonephritis or reflux nephropathy that are characterized by shrunken kidneys with uneven surface. Pyelocaliceal system of the kidneys remains unaffected in patients with Balkan nephropathy, unlike the characteristic changes observed in pyelonephritis or obstructive nephropathy. Absence of papillary necrosis/calcifications also enables differentiation of Balkan nephropathy from analgesic, obstructive, reflux nephropathy [110, 115].

Recently similarity of Balkan nephropathy and nephropathy induced by Chinese herbs used in slimming diets have been suggested [48]. Nevertheless, Chinese herb nephropathy is rapid progressive tubulointerstitial diseases with pronounced fibrosis and progression towards end-stage renal disease within few years, clearly different from the protracted clinical course of Balkan nephropathy.

Prevention and treatment

Balkan nephropathy is a disease of unknown etiopathogenesis, so that recommendations regarding effective prevention are not possible. Efforts have been made to improve the living conditions, bring high quality drinking water to endemic villages and undertake other hygienic measures. Treatment is planned according to the stage of the disease. In principle, the treatment involves the measures for slowing down deterioration of renal function and those applied in chronic renal failure [116].

End-stage renal disease is treated with dialysis and kidney transplantation. Hypertension and cardiovascular diseases affect the Balkan nephropathy patients less frequently, so they tolerate hemodialysis rather well compared to patients with other renal diseases. The Balkan nephropathy patients on long-term hemodialysis frequently develop upper urothelial or urinary bladder carcinoma.

Although the number of reported cases with kidney transplant is small, neither specific post-transplantation problems nor disease recurrency on the transplanted kidney have been described.

However, recent studies indicated that patients with Balkan nephropathy are at increased risk for the development of upper urothelial tumors in both native and transplanted kidneys [117].

Overview of clinical and laboratory studies

Balkan nephropathy is a chronic tubulointerstitial disease with insidious occult onset progressing without symptoms. Agreement as to how to define the early asymptomatic phase of the disease is lacking, since no specific indicators for the diagnosis have been recognized. The diagnosis is established according to epidemiological criteria (farmers in endemic villages, familial history positive for endemic nephropathy), presence of tubular proteinuria, findings of symmetrically shrunk kidneys with smooth surface, without calcifications and ruling out of other renal disease. Renal biopsy may make the diagnosis easier, although the changes are non-specific. One of the important features of Balkan nephropathy is its association to high incidence of tumors of the renal pelvic and ureters, comparable to analgesic nephropathy (se chapter 17) and aristolochic acid nephropathy (see chapter 33).

So far, laboratory studies have failed to detect any disorder as a specific marker for early detection of the disease or a reliable indicator for differential diagnosis. Laboratory studies have confirmed that Balkan nephropathy is a tubulointerstitial disease so that tubular disorders precede impairment of glomerular

filtration. Although anemia is one of the criteria for the diagnosis of the disease, it has not been evidenced that pathogenesis and features of this anemia differ from that observed in other chronic renal diseases. It is only more severe in end-stage Balkan nephropathy patients than in patients with other kidney diseases.

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