EARLY DETECTION OF BALKAN ENDEMIC NEPHROPATHY IN BOSANSKA POSAVINA

Enisa Mešić

Internal Clinic, Departement for Nephrology, University of Tuzla,
Clinical Center, Trnovac bb 75000 Tuzla, Bosnia and Herzegovina

* Corresponding author

Abstract

Balkan endemic nephropathy (BEN) is a chronic tubulointersticial nephropathy that is diagnosed in a few agrarian regions of Balkan. Even tough numerous dilemmas and conflicting opinions regarding BEN etiology are encountered in literature, prevailing theory is that BEN is caused by chronic poisoning with aristolochic acid ingested by food in people with genetic predisposition to this disease. BEN is categorized as a toxic tubulointerstitial nephropathy, with clinical picture and disease progression not differing from other tubulointerstitial nephropathies, but with insidious and gradual progression to end stage renal disease. There is no specific and sensitive diagnostic biomarkers for BEN and we use epidemiological and functional diagnostic criteria. It is considered that BEN affects up to 10% of population in endemic region. According to Renal Register of Bosnia and Herzegovina, there are around 15 % of BEN patients on chronic dialysis program, but no official data on the number of predialysis BEN patients, because of lack of adequate demographic data and screening or systematic examinations of the population living in the affected region since 1991. The members of the Society of nephrology, dialysis and transplantation of Bosnia and Herzegovina organized screening in two villages of Bosanska Posavina, as a part of the "Program Program of detection of chronic kidney diseases in high-risk population in Bosnia and Herzegovina", project which was approved from International Society of nephrology. In this paper we analyze preliminary results of that Program and discuss previous studies about BEN in Bosnia and Herzegovina, particularly diagnostic criteria and biomarkers of BEN.

KEY WORDS: Balkan Endemic Nephropathy, diagnostic criteria, biomarkers

Introduction

Balkan endemic nephropathy (BEN) is a chronic irreversible tubulointersticial nephritis still of unknown etiology that is diagnosed in a few agrarian regions of Balkan (Bosnia and Herzegovina, Bulgaria, Croatia, Romania, Serbia). Majority of endemic villages are located at alluvial valleys of rivers, Danube tributary rivers. There were no significant changes in the geographic characteristics of BEN distribution since the first disease descriptions in 60tees of twentieth century (1). The villages that were affected with the disease in the past are still endemic BEN regions, while non-endemic villages, sometimes located in close proximity to them, still have no cases of the disease registered. Today, BEN is usually diagnosed in adult population, between 50 and 70, with slight predominance of female patients. Disease is characterized by frequent occurrence of tumors of renal pelvis and urethers.

BEN affects only village dwellers, farmers, but is not spread in all villages; some endemic villages are only few kilometers away from non-endemic ones. The family character of the disease is described, but the mechanism of inheritance is not fully understood. Often, a few members of one family, precisely of one household, become ill, in one or more generations. In endemic village, there are also many non-endemic households, and they all live in close proximity to endemic families (households). Until now, the disease was not diagnosed in children.

Even tough numerous dilemmas and conflicting opinions regarding BEN etiology are encountered in literature, prevailing theory is that BEN is caused by chronic poisoning with aristolochic acid ingested by food in people with genetic predisposition to this disease. The dA-aristolactam and dG-AL DNA adducts are isolated in renal cortex of BEN patients, but not in patients with other chronic renal diseases (3). Therefore, BEN is categorized as a toxic tubulointerstitial nephropathy, with clinical picture and disease progression not differing from other tubulointerstitial nephropathies (1), but with BEN having insidious and gradual progression to end stage renal disease. The thing that makes this disease so mysterious is not primarily the fact that the etiology is still unknown, but its unique epidemiologic characteristics, that is focal nature of its occurrence (1,4). It is considered that BEN affects up to 10% of population in endemic region (5). According to the estimates, Bosnia and Herzegovina had around 2000 registered BEN patients before 1992 (6). Unfortunately, current data on the number of inhabitants of Bosanska Posavina affected by BEN is not known, except the data on the number of BEN patients receiving chronic dialysis. Percent of those patients is around 15 % and is stable (7).

Diagnostic criteria

It is not an easy task to diagnose BEN in early, asymptomatic stage of the disease. Even when decline in renal function exists, the symptoms of the disease are not specific. Diagnosing BEN is not simple even in advanced stages of renal insufficiency, because clinical picture is interpolated by other risk factors like obesity, hypertension, smoking, alcohol consumption, and other renal diseases as well. Until now, no specific biomarker for diagnosis of BEN is found. Pathohystological findings confirm tubulointersticial nephropathy, exclude other possible renal lesions, but have no influence on choice of therapy. Therefore, a renal biopsy is performed in a very limited number of patients with BEN suspicion, for example, in subjects with family burden for BEN who do not live in endemic village, emigrants, immigrants, or in subjects suspected of having some other renal disease despite of present criterion for diagnosis of BEN (overt proteinuria). These are the reasons why today the BEN is diagnosed if certain agreed diagnostic criterions are met and after excluding other possible renal diseases.

Basic criteria for diagnosis of BEN were according to Danilovic (8): working in agriculture in affected regions, positive family history of renal disease, proteinuria (low grade, usually intermittent), low specific gravity of urine, anemia and high blood urea nitrogen. Those were criteria that were, with critical approach and periodical revisions, applied for a few decades, until 2008, when they were replaced by criteria agreed on during The International meeting on diagnostic criteria for BEN, which was held as a part of Croatian Nephrology Congress on Brač, in a form of "Consensus Statement. International Workshop on Screening, Diagnosis, Classification and Treatment of Endemic (Balkan) Nephropathy" (9) .

It was agreed that, above all, in diagnosing, defining, and classification of BEN, existing internationally accepted criterion for diagnosis and classification of chronic kidney diseases (CKD) should be used (10, 11).

Commission for International Association of Nephrologists for Global Improvement in Nephrology (COMGAN), in purpose of early detection and prevention of CKD, accepted those recommendations and suggested utilization of MDRD (Modification of Diet

in Renal Disease) formula for estimating glomerular filtration rate (GFR) (12), with necessity of standardized and calibrated measurement of serum creatinine. Aforementioned Consensus (9) suggests classification of a subject as a BEN positive if next criteria are met: increased tubular proteinuria (alfa 1 microglobulin-α1MG), positive history for previous renal disease or carcinoma of urothelium, positive family history, that is disease in the household.

Basic screening for BEN assumes getting answers for next questions: weather subject lives in an endemic village for more than 20 years, weather the subject lives in the affected household for more than 15 year, is there a proximal tubular proteinuria (α1MG), decreased renal function (estimated GFR below expected for given sex and age and/or albumin to creatinine ration in urine above cut off value), urothelial carcinoma, and if subject is treated for any other disease that could cause chronic renal disease. Since frequency of tumors of proximal urinary tract in BEN regions is high, early diagnosis is of great importance. Citological examination of urinary sediment is a simple method used for diagnosing non-papillary and urothelial carcinoma in situ with substantial sensitivity (47-97% in different studies) (13,14).

BEN should be out ruled as a possible diagnosis in individuals with CKD of unknown origin or with urothelial carcinoma, but living outside the endemic region, in members of families affected by BEN also living outside an endemic region. However, we should always bear in our mind potential existence of sporadic cases of BEN in non-endemic regions (15). BEN should be excluded in individuals with positive history of exposure to nephrotoxic agents, including nonsteroidal antireumatics, plants containing aristolochic acid, lead, cadmium. Usual pathohystological finding in BEN patients is extensive hypocellular interstitial fibrosis in concordance with tubular atrophy (16). Therefore, the diagnosis of BEN could be confirmed (or diagnosis of other renal disease excluded) pathohystologicaly, but it is not ethically justified to perform a biopsy to all subjects suspected of having BEN.

Through all these years, different criteria were suggested or added to the accepted diagnostic criteria for BEN, in order to improve diagnosing BEN in its early stages. Among others, there were decreased kidney volume and shorter longitudinal diameter of the kidney found on ultrasonography (according to age, sex, body mass index, height). Anemia, more profound than expected for given stage of CKD, was considered for a long time as one of the criteria for diagnosing early stages of BEN (17, 18). However, in the recent times its role in early diagnosis of BEN is questioned (19, 20). Djukanovic et al compared epidemiological, clinical and functional markers in BEN and concluded that proteinuria, concentration urine concentration of α1MG and kidney length (volume) were significant predictors of BEN (19).

After screening and other necessary diagnostic procedures, the results could be classified into four groups. The first one consist of those diagnosed with BEN (pathohystological confirmation or living in an endemic village for more than 20 years with tubular proteinuria, lower GFR and anemia or living in an endemic household with tubular proteinuria or living in an endemic village for more than 20 years with tumor of urothelium and tubular proteinuria). The second group consists of subjects suspected for BEN (living in an endemic household for more than 15 years with lower GFR and anemia or living in an endemic village for more than 15 years with tubular proteinuria or living in an endemic village for more than 20 years with tumor of urothelium). The third group consists of subjects with high risk for BEN (living in an endemic household for more than 15 years), and the fourth are sporadic cases of BEN confirmed by biopsy in non-endemic regions. Renal function in BEN patients is classified according to National Kidney Foundation (NKF) classification (11).

According to recommendations of KDIGO (Kidney Disease: Improving Global Outcomes) guidelines (10, 11) GFR should be estimated utilizing MDRD formula, while Cockroft-Gault equation proved less accurate in healthy subjects than in patients with CKD. It is also noticed that this equation offers less accurate information in elderly, and also overestimates GFR when renal function is seriously impaired. Likewise, MDRD equation has some limitations, for example it underestimates GFR in individuals with normal serum creatinine levels, thus, may erroneously categorize certain healthy subjects as having CKD. Hence, it is advisable to report exact GFR value, and not the stage of CKD, especially in case of estimated GFR < 60 ml/min. Also, usage of age and gender-specific lower limits of normal GFR values are proposed and tables with reference values of GFR in a European Caucasians population are offered (21). Overall, early diagnosis of BEN could not be made without positive family history for BEN, without data on longstanding living in endemic region, more

accurately household, and without proof of tubular proteinuria. Differential diagnosis are any other chronic tubulointerstitial nephropathy, especially analgetic nephropathy, and those caused by aristolochic acid, chronic intoxication by metals (lead, lithium, cadmium, arsenic) or medications (cyclosporine, tacrolimus, analgetics, pamindronat, antibiotics).

Biomarkers

Way back, a famous epidemiologist from Bosnia and Herzegovina, professor Gaon, in 1976, wrote that BEN, just like other diseases, results from action of multiple causes related to an unknown agent, environmental factors and host- Gordon's triad (22). One of the suggestions for reducing incidence of BEN was organized perlustration (screening) for albuminuria in endemic region.

In endemic village, Pisari (five kilometers from Bosanski Šamac, located on the right riverbank of Bosnia River) screening of inhabitants was conveyed as a part of Action Republic Program (23). Total number of 328 inhabitants was screened, 139 male and 189 female, and pathological urine was found in 12.8 % of cases (42 examinees). Protein electrophoresis confirmed a tubular proteinuria in 26 examinees (61.9 %) with pathological urine (24, 25). Republic Action Program predicted screening of around 300000 inhabitants in six northern Bosnian municipalities (Bijeljina, Brčko, Bosanski Šamac, Orašje, Modriča and Odžak) through screening for proteinuria (sulfosalicilic acid and strips) in all examinees in the first phase. In the first year of conducting this plan, 98583 inhabitants were examined, out of which 4.66 % were positive for proteinuria (23). Authors believed that the actual number of inhabitants with proteinuria was substantially higher, but were not able to prove that on the field with current methods of detection. In 20 endemic settlements (Lazarevac municipality) in Serbia, 23645 inhabitants were examined in the same time, and proteinuria was confirmed in 3395 (14.36%) of them (26).

KDIGO guidelines (12) suggest usage of any spot urine specimen (first morning urine specimen is preferred, but not mandatory), and presentation of results in a form of albumin to creatinine ratio in urine (ACR). However, many nephrologists share opinion that it is sufficient to determine albuminuria only (27, 28). It is of significance for Bosnia and Herzegovina for purpose of a field work and screening of population. There are a scarce number of studies that examined kidney function in detail in early phase of BEN. Mainly, it was proved that primary lesion in BEN affects proximal tubule (18). In one of the studies completed in 1987 the functional tests were conducted with purpose of estimation of renal function in a small group of examinees with positive family history for BEN, and it led to the conclusion that they had preserved global and partial renal function with compensatory adaptation of functioning nephrons (exaggerated natriuresis, excretion fraction of sodium on the upper limit of normal values, high maximal urine osmolality) (29). Radonic in 1992 also describes changes in urine concentration ability, occurring some time before decease in renal blood flow and GFR (30). The observation that increased renal loss of salt, increased excretion of uric acid, damaged urine acidification, glicosuria and aminoaciduria also exist, all suggest the lesion of proximal tubules (17, 18).

Other potential urinary markers for BEN were also tested, such as neopterin (31) and glycosaminoglycanes (32), but still did not prove as sensitive, specific and useful tests for detection of early stages of BEN. In Bosnia and Herzegovina kidney function of BEN patients in early stages of disease was examined in late 90tees of twentieth century. There were 59 patients with pathohystologically confirmed diagnosis. Authors concluded that average kidney volume was bellow referent borderline values in all patients, even in the group (11 patients) with average GFR of 120.65 ml/min (33).

Regardless of all former efforts, we still do not have sufficiently good, accurate and simple test that would be appropriate urinary marker for diagnosing of BEN. Ideal test, except the fact that it should be sensitive and specific enough, must be cheap, easily applied for mass screening of population and routine clinical exam. It is proved that tubular proteinuria is one of the early signs of BEN. There are a few protein markers of low molecular weight suggesting tubular damage. In accordance with our former studies (34), recent studies of cadmium nephropathy in Japan (35) and in BEN (36, 19), it seems that α1MG is the best marker of tubular damage in BEN.

One of the main characteristics of BEN is a proximal tubular dysfunction. Beta 2 microglobulin (β2MG) was considered a sensitive marker of tubular lesion for a while, and it was used in screening for BEN (37, 38). However, since it did not proved as reliable marker (including instability in low pH an in room temperature), nephrologists were seeking for better and more reliable marker and finally turned to α1MG. It is believed that single determination of α1MG is acceptable for screening purposes, if urine has certain

density (specific gravity between 1010 and 1030) (35). In general, the cut off value of 17 mf/24 h for α1MG (39), or 5 mg/l (40) is suggested. For purpose of BEN screening, suggested cut off value is 15 mg/g of creatinine (41), and 14 mg/g of urine creatinine. The aim of one study was the estimation of urinary α1MG and albumine ratio, and it was concluded that the cut off value was 0.9, with higher values speaking in favor of predominantly tubular proteinuria (41). It is noticed that increased systolic blood pressure can influence urinary excretion of α1MG (42), which in turn requires considering not only sex and age, but also blood pressure, for clinical estimation of renal dysfunction.

Suggested sex-specific cut off values for albumin/creatinine ratio in urine were 17 and higher ηg/mg for men and 25 and higher ηg/mg for women (43). For albuminuria, suggested values are higher than 30 mg/24 h, which is higher than 10 mg/l in mass screening (28). In one study in Bosnia, median of the values for albuminuria in BEN patients was 11.6 mg/l (44). If the values were higher than suggested, proteinuria in 24 h (timely urine specimen) is advisable.

Screening for chronic kidney disease in Bosanska Posavina in 2009 (EDCKD-BH)

Prevalence of BEN was stable through the past decades, however, in the last ten years in literature, as well as in the oral presentations on nephrological meetings, we can encounter an opinion that the incidence and prevalence of BEN are in slow decline, while other authors believe that the incidence remains the same (45, 46). Radovanović in 1991 expresses his opinion that it is yet obvious that the development of BEN is slower, lasts longer and that manifestations of the disease moves toward older age groups, meaning less intensive contact with supposed toxic agent, cause of the disease, thus rendering future decline in its incidence and prevalence. However, bearing in our mind all the present knowledge on BEN, it seems that the disease has had an endemic-epidemic character in the past, and therefore we can count on potential new epidemic wave in the future (47).

According to Renal Register (48) there are around 15 % of BEN patients on chronic dialysis program in Bosnia and Herzegovina. However, Bosnia and Herzegovina does not have official data on the number of BEN patients that are still not in terminal stage of renal insufficiency, and the number of individuals in risk is also hard to estimate, firstly because of lack of adequate demographic data, and secondly because of the lack of screening or systematic examinations of the population living in the affected region since 1991.

Those were the reasons why the Society for Nephrology, Dialysis and Transplantation of Bosnia and Herzegovina (UNDTB&H) justified and commenced a screening program for hypertension, diabetes and BEN. At the end of 2009, UNDTBiH applied with project under the title "Program of early detection of chronic kidney disease in high-risk population of Bosnia and Herzegovina (EDCKD-BH)" for Non-communicable Chronic Disease Prevention Programs in Developing Countries, ISN Research Committee, that was accepted, and its successful realization will be of great help in solving numerous dilemmas regarding BEN in Bosnia and Herzegovina. Members of UNDTB&H have already started realization of aforementioned Program, already in two villages of Bosanska Posavina, one known endemic village Domaljevac and second non-endemic village Svilaj, both located near Sava River, separated by 30 kilometers from each other, in close proximity of Odžak town. Between those two villages there were no geophysical differences in field characteristics found.

Endemic village Domaljevac is a big village, with estimated number of inhabitants is around 4000, while non-endemic village Svilaj has around 1000 inhabitants. Inhabitants got a general call for health checkup that included taking history, physical exam, urine dipstick test (Combur-Test Urine test strips, Cobas, Roche) and urine test for microalbuminuria in those with negative proteinuria (Micral-Test, ACCU-CHEK, Roche). Screening was done by the nephrologists from a clinical institution, medical students, local physicians and nurses. The checkup was done in endemic Domaljevac, with massive response counting 387 inhabitants (around 10 % of total village population), between 9 an 91 years old, while in non-endemic Svilaj it was 217 inhabitants (around 20 % of total village population), between 13 an 90 year old. In both those villages, over 60% of examinees were women (Domaljevac around 65 % and Svilaj around 62 %). During examination of Domaljevac inhabitants, 149 (38,5 %) of them claimed that they are coming from families with positive history for BEN. In Svilaj, non-endemic village, there were also some examinees with family burden for BEN (20 or 9,2 %). Those were mainly women that have moved from their native villages into Svilaj after getting married. Those examinees were excluded from further statistical analysis. In endemic village Domaljevac, total of 187 exam-

inees had proteinuria or microalbuminuria (43.32 %) in contrast to 71 (36,04 %) examinees from non-endemic village Svilaj. Out of 149 examinees from Domaljevac, with family burden for BEN, 43 of them had proteinuria (28,86 %), and out of those 106 negative for proteinuria, 42 had microalbuminuria (28,19 % of 149 examinees), that is total of 85 (57,05 %) examinees with proteinuria and microalbuminuria. Out of 229 inhabitants of Domaljevac without family burden for BEN, 47 (20,52 %) had proteinuria, while out of 182 without proteinuria, 55 were positive form microalbuminuria (24,02% out of 229 examinees). Totally, 102 inhabitants (44,54 %) had positive proteinuria and microalbuminuria. In non-endemic Svilaj there were 26 inhabitants with positive proteinuria out of 197 examined (13,2 %), and out of 171 examinees negative for proteinuria, 45 had positive microalbuminuria (22,84 % out of 197 examined). There was total number of 71 inhabitants with positive proteinuria or micoralbuminuria in Svilaj (36,04 %). The number of examinees with proteinuria and microalbuminuria in endemic Domaljevac was statistically significantly higher in the group with family burden compared to the group without family burden (85 out of 149 and 102 out of 229, Fisher's exact test p=0,02) in contrast to examinees form non-endemic Svilaj (85 out of 149 and 71 out of 197, Fisher's exact test p=0,0001). But the number of inhabitants with proteinuria and micoralbuminuria did not significantly differ when group from endemic Domaljevac without family burden and group form non-endemic Svilaj were compared (102 out of 229 and 71 out of 197, Fisher's exact test, p=1,00). When we compare only inhabitants with positive microalbuminuria, there is no statistically significant difference between any of the groups. In three-years study of professor Gaon et al (49) in early 90tees of twentieth century, the prevalence rate of albumin positive subjects in endemic village Gornja Crkvina near Bosanski Šamac was 14.5 % for men and 13.6 % form women, while in non-endemic village Lugovi the number of albumin positive subjects was very small (0.024 % out of 246 examined). In other earlier study, Tulumović et al found frequency of proteinuria to be 39 % in endemic village Pisari, which was tubular proteinuria of 24% (25). Through our screening program, we have found frequency of microalbuminuria to be 25,7 % in endemic village Domaljevac and 22,8 % in non-endemic village Svilaj. We should stress the fact that in our study the target population was extracted from the general population with purpose of screening for risk of CKD in general, not for BEN exclusively. In both mentioned villages, a substantial number of hypertensive subjects was registered and around 12% (endemic Domaljevac) and 9% (non-endemic Svilaj) diabetics. Hypertension (over 140/80 mmHg) was registered in 59% of inhabitants of endemic Domaljevac and 33,5% of inhabitants of non-endemic Svilaj. The greatest frequency of hypertension was registered in a group consisting of 149 inhabitants of endemic Domaljevac with family burden for BEN (74,5%). Mentioned percentages could not be considered indicative for number of hypertensive patients estimate in examined population, neither as part of BEN, nor as part of other chronic noncommunicable diseases. That is because, in our opinion, responders for screening were primarily subjects already treated for hypertension, heart disease, diabetes or those aware of their higher risk for those conditions, as well as for BEN. Nevertheless, other investigators have registered higher frequency of hypertension in endemic regions, even though hypertension was never considered patognomonic form BEN, even in overt renal insufficiency. Likewise, in recent studies it was proved that prevalence of hypertension in endemic villages resembled that in non-endemic ones (52 % and 49 %, respectively) (50, 51). Arsenović et al have registered hypertension in 43 % of endemic family's members and in 35 % of members of non-endemic families (50). Authors explained their findings by advanced age and high prevalence of obesity among examinees. Bulgarian study also showed higher frequency of hypertension in offspring of BEN patients (52). All examinees with positive proteinuria or microalbuminuria, other pathological urine finding or hypertension were potential candidates for second phase of study, that is for more detailed examination of kidney function in purpose of revelation of causative factor for proteinuria/microalbuminuria or hypertension. Diabetics were referred for additional treatment in family medicine service. Since mentioned results of conveyed screening are just a start of the "Program of detection of chronic kidney diseases in Bosnia and Herzegovina", we should not pull any conclusions on number of BEN patients or other CKD in region of Bosanska Posavina without further screening and mass population investigations. Meanwhile, conclusion remains that there is a very high percentage of hypertensive subjects and subjects with proteinuria/microalbuminuria registered in the examined population of Bosanska Posavina, which is the facts that concerns and confers a need for prompt and efficient further measures for realization of "Program for detection of chronic kidney diseases in Bosnia and Herzegovina".

References

(1) Bamias G., Boletis J. Balkan Nephropathy: Evolution of Our Knowledge. AJKD 2008; 52:606-616

(2) Grollman A.P., Jelaković B. Role of environmental toxins in endemic (Balkan) nephropathy. JASN 2007; 18: 2817-2823.

(3) Grollman A.P., Shibutani S., Moriya M., Miller F., Wu L., Moll U. et al. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. PNAS 2007; 104: 12129-12134.

(4) Josić D. Endemska nefropatija u području Brodsko-posavske županije. Hrvatski časopis za javno zdravstvo 2006; 2: broj 7; accesed online at http://www.hcjz.hr/clanak.php?id=12904

(5) Silva F.G. Chemical-induced nephropathy: A review of the renal tubulointerstitial lesions in humans. Toxicol. Pathol. 2004; 32 (Suppl 2): 71-84.

(6) Trnačević S., Halilbašic A., Imamović G., Mešić E. Balkan endemic nephropathy in Bosnia and Herzegovina. Facta Universitatis series Medicine and Biology 2002; 9: 31-33.

(7) Mešić E., Resić H,. Halilbašić A., Komljenović I., Vasilj M., Vucicevic .L, Trnačević S. Renal replacement therapy in Bosnia and Herzegovina: report of the Society of nephrology, dialysis and transplantation of Bosnia and Herzegovina. Nephrol. Dial. Transplant. 2003; 18: 661-663.

(8) Danilović V. Diagnosis of endemic nephropathy. Radovi XLVIII ANU BiH 1973; 17: 53-64.

(9) Anonymous. Consensus Statement. International Workshop on Screening, Diagnosis, Classification and Treatment of Endemic (Balkan) Nephropathy. Island of Brač, Croatia, April 2008.

(10) Anonymous. National Kidney Foundation: KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. AJKD 2002; 39 (Suppl 1): S1-S266

(11) Levey A., Eckardt K.U., Tsukamoto Y., Levin A., Coresh J., Rosert J., De Zeeuw D., Hostetter T., Lamiere N., Eknoyan G. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005; 67: 2089-2100.

(12) Levey S., Atkins R., Coresh J., Cohen E.P., Collins A.J., Eckardt U.K., et al. Chronic kidney disease as a global public health problem: Approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007; 72: 247-259.

(13) Rathert P.. Urinary cytology in cases of bladder cancer: a critical evaluation. Urologe A 2003; 42: 908-911

(14) Brown F.M. Urine cytology. It is still the gold standard for screening? Urol. Clin. North. Am. 2000; 27: 25-37

(15) Nikolic J. Epidemijska nefropatija i tumori gornjeg urotela. Sporadična endemska nefropatija. Izdavacko preduzece Beograd A.D. 2006; 171-181.

(16) Ferluga D., Hvala A., Vizjak A., Trnačević S., Halilbašić A. Renal function, protein excretion and pathology of Balkan endemic nephropathy. III Light and electron microscopic studies. Kidney Int. 1991; 40 (Suppl 34): S57-S67.

(17) Stefanović V. Balkan endemic nephropathy: a need for novel aetiological approaches. QJ Med 1998; 91: 457-463.

(18) Stefanović V., Jelaković B., Cukuranović R, Bukvić D., Nikolić J., Lukić Lj., Gluhovschi G., Toncheva D., Polenaković M., Cosyns J.P. Diagnostic Criteria for Balkan endemic nephropathy: Proposal by an international panel. Ren. Fail. 2007; 867-880.

(19) Djukanović L., Marinković J., Maric I., Lezaić V., Dajak M., Petronic D., Matic M,, Bukvic D. Contribution to the definition of diagnostic criteria for Balkan endemic nephropathy. Nephrol. Dial. Transplant. 2008; 23: 3932-3938

(20) Mesić E. Renal anemia in the dialysis patients with Balkan nephropathy. Recent advances in Balkan endemic nephropathy research, Beograd 2007, p 26.

(21) Wetzels J., Kiemeney L., Swinkels D., Willems H., den Heijer M. Age and gender specific reference values of estimated GFR in Caucasians: The Nijmegen Biomedical Study. Kidney Int. 2007; 72: 632-637.

(22) Gaon J., Pokrajčić B., Durić E. Uticaj nekih faktora spoljne sredine na odrzavanje endemske nefropatije i prijedlog za primjenu nekih preventivnih mjera. Acta Med. Salin. 1976; 5 (2): 109-118.

(23) Fajgelj A., Filipović A., Popović N. Akcioni republicki program rjesavanja problema endemske nefropatije u SR BiH (Rezultati poslije prve godine njegove primjene). Acta Med. Salin. 1976; 5 (2): 57-65.

(24) Halilbašić A., Martinović K., Pavlićević A., Mehikić S., Nakićević M., Pašić R., Selesković H., Pašić I. Neki poremecaji biohemizma krvi kao moguci indikatori lezije bubrega kod stanovnika sela Pisari. Acta Med. Salin. 1976; 5 (2): 163-167.

(25) Tulumović T., Mijatov S., Andjelić M., Smajić A., Pavlićević A., Mehikić S., Malešević M., Poljaković Dz., Sušić H., Pašić I. Korelacija radiorenograma, urina i elektroforeze urina kod ispitanika sela Pisari. Acta Med. Salin. 1976; 5 (2): 169-172.

(26) Danilović V., Naumović T., Velimirović D. Dijagnoza i lečenje endemske nefropatije. Acta Med. Salin. 1976; 5 (2): 127-133.

(27) Jafar T., Chaturvedi N., Hatcher J., Levey A. Use of albumin creatinine ratio and urine albumin concentration as a screening test for albuminuria in an Indo-Asian population. Nephrol. Dial. Transplant. 2007; 22: 2194-2200;

(28) Gansenvoort R., Heerspink L., Witte E. Methodology of screening for albuminuria. Nephrol. Dial. Transplant. 2007; 22: 2109-2111.

(29) Vukusić Z., Radenković S., Tasić S., Trajkovski S., Raičević R. Funkcionalno stanje bubrega u ispitanika sa endemskog zarista bez klinicki manifestnog oboljenja. Etiology of endemic (Balkan) nephropathy. Proceedings of the 6th Symposium on endemic (Balkan) nephropathy, Niš 1987;153-158.

(30) Radonić M., Radošević Z. Clinical features of Balkan endemic nephropathy. Food Chem. Toxicol. 1992; 30: 189-192.

(31) Toncheva D., Galabov A.S., Laich A. Urinary neopterin concentrations in patients with Balkan endemic nephropathy. Kidney Int. 2003; 64: 1817-1821.

(32) Juretić D., Čvorišcec D., Vuković-Holjevac A., Benković J., Lipovac K., Stavljenić A. Urinary glycosaminoglycans in different phases of Balkan endemic nephropathy. Nephron. 1993; 65: 564-567.

(33) Trnačević S., Halilbašić A., Ferluga D., Plavljanić D., Vizjak A., Duraković H., Habul V., Mešić E., Imamović G., Hranisavljević J., Pašić M., Paunović G. Renal function, protein excretion and pathology of Balkan endemic nephropathy. I Renal function. Kidney Int. 1991; 40 (Suppl 34): S49-S51.

(34) Raičević S., Trnačević S., Hranisavljević J., Vucelić D.. Renal function, protein excretion and pathology of Balkan endemic nephropathy. II Protein excretion. Kidney Int. 1991; 40 (Suppl 34): S52-S56.

(35) Ikeda M.., Ezaki T., Tsukuhara T., Furuki K., Fukui Y., Okamoto S., Ukai H., Sakurai H., Shimbo S., Ikeda M. Reproducibility of urinary cadmium, alpha-1-microglobulin and beta2-microglobulin levels in health screening of the general population. Arch. Environ. Contam. Toxicol. 2005; 48: 135-140.

(36) Kos J., Miletić-Medved, Cvoriščec D., Sertć J., Kovač-Peić A.M., Pecin I., et al. Characteristics of the population from a Croatian focus of endemic nephropathy. Coll. Antropol. 2006; 30 (Suppl 1): 51.

(37) Hall P.W., Vasiljević M. Beta 2 mikroglobulin excretion as an index of renal tubular disorders with special reference to endemic Balkan nephropathy. J. Lab. Clin. Med. 1973; 81: 897-904.

(38) Stefanović V., Mitić-Zlatković M., Cukuranovic R., Miljković P., Pavlović N.M, Vlahović P. Beta 2 mikroglobulin in patients with Balkan nephropathy and in healthy members of their families. Kidney Int. 1991; 40 (Suppl. 34) S 97-S101.

(39) Bergon E., Granados R., Fernandez-Segoviano P., Miravalles E., Bergon M. Classification of renal proteinuria: a simple algorithm. Clin. Chem. Lab. Med. 2002; 40: 1143-1150.

(40) Ikeda M., Ezaki T., Tsukahara T., Moriguchi J., Furuki K., Fukui Y., et al. Critical evaluation of alpha 1 and beta 2 mcroglobulins in urine as markers of cadmium-induced tubular dysfunction. Biometals 2004; 17: 539-541.

(41) Čvoriščec D. Early diagnosis of endemic nephropathy. Clin. Chim. Acta 2000; 297: 85-91.

(42) Vyssoulis G.P., Tousoulis D., Antaniades C., Dimitrakopoulos S., Zervoudaki A., Stefanadis C. Alpha 1 microglobulin as new inflamatory marker in newly diagnosed hypertensive patients. Am. J. Hypertens. 2007; 20: 1016-1021.

(43) Mattix H., Hsu C.Y., Shaykevich S., Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: Implication of sex and race. JASN 2002; 13: 1034-1039.

(44) Imamović G., Batuman V., Mešić E,. Trnačević S. Microalbuminuria as a potential marker of susceptibility to Balkan endemic nephropathy. Coll. Antropol. 2006; 30 (Suppl 1): 54.

(45) Dimitrov P.S., Simeonov V.A,. Stein A.D. Balkan endemic nephropathy in Vratza, Bulgaria, 1964-1987: an epidemiologc analysis of population-based disease registers. Eur. J. Epidemiol. 2001; 17: 847-853.

(46) Djukanović L., Bukvić D, Marić I., at al. Open questions on Balkan nephropathy. Nephrol. Dial. Transplant. 2001; 16(Suppl 6): 27-29

(47) Radovanović Z. Epidemiological characteristics of Balkan endemic nephropathy in eastern regions of Yugoslavia. IARC Sci Publ 1991; 11: 20)

(48) Resić H., Mešić E. Renalni registar BiH 2001-2005. Udruženje za nefrologiju, dijalizu i transplantaciju u BiH. Sarajevo 2007.

(49) Gaon J., Turić A., Gaon D., Aganović I., Verbić D., Golemac S. Rezultati trogodišnjeg ispitivanja raširenosti i ekologije endemske nefropatije u seoskim naseljima Gornja Crkvina i Lugovi (Bosanski Šamac). Etiology of endemic (Balkan) nephropathy, Proceedings of the 6th Symposium on endemic (Balkan) nephropathy, Niš 1987; 27-34.

(50) Arsenović A., Bukvić D., Trbojević S.,, Marić I., Djukanović L. Detection of renal dysfunctions in family members of patients with Balkan endemic nephropathy. Am. J. Nephrol. 2005; 25:50-54,

(51) Pecin I., Miletić-Medved M., Jovanović A., et al. Prevalence, treatment and control of hypertension in a Croatian focus of EN-comparison with epidemiology of hypertension (EHUH) study results. Coll. Antropol. 2006; 30 (Suppl.1): 55.

(52) Dimitrov P.S., Simeonov V.A., Tsolova S.D., Bonev A.G., Georgieva R.B., Karmaus W.J. Increased blood pressure in adult offspring of families with Balkan endemic nephropathy: a prospective study. BMC Nephrology 2006; 7: 12.