Open questions on Balkan nephropathy

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Balkan endemic nephropathy (BEN) is a chronic tubulointerstitial disease prevalent in some parts of south-eastern Europe with Central Serbia as the most affected region. In spite of numerous studies on the subject, many features of Balkan nephropathy have remained unelucidated.

Is BEN tapering off?

The prevalence of the disease was stable over many years, but now appears to decline in most affected settlements [1]. Some authors also suggest that the incidence of BEN decreases [1,2] and that it appears to be tapering off; others, however, describe a stable incidence of BEN [3]. The question arises on different epidemiological characteristics of the disease in different endemic regions. In search of an answer to this question a retrospective analysis of the incidence of haemodialysis BEN patients was undertaken in four haemodialysis centres situated in three different endemic regions over the period 1991–2000. The medical files of haemodialysis patients treated in Lazarevac (Kolubara River), Nis and Leskovac (South Morava River) and Pozarevac (Pek River) were used in this study. The incidence of haemodialysis patients with BEN from endemic villages was compared with the incidence of patients suffering from other renal diseases and living in the same endemic villages over the period 1991–2000. The medical files of haemodialysis patients treated in Lazarevac (Kolubara River), Nis and Leskovac (South Morava River) and Pozarevac (Pek River) were used in this study. The incidence of haemodialysis patients with BEN from endemic villages was compared with the incidence of patients suffering from other renal diseases and living in the same endemic villages.

The incidence of BEN patients in ESRD who started haemodialysis was different in three endemic regions already known as differently affected endemic foci. However, during the last decade the incidence of haemodialysis BEN patients remained stable in all three regions (Figure 1a). In the same period, the incidence of haemodialysis patients suffering from other renal diseases and living in the same endemic villages (mean incidence for three regions 0.035–0.28) was lower than the incidence of BEN patients on haemodialysis (0.22–0.58) (Figure 1b). These results correspond with those reported by Ćukuranovic et al. [4] but these authors pointed out a marked decrease of the incidence of BEN in end-stage renal disease (ESRD) in the last 10 years as compared with the previous decade. BEN is a slowly progressive disease and patients usually start haemodialysis in their sixties. Therefore, although our data demonstrate a stable incidence of BEN in ESRD it only indicates that BEN is preserved. In order to answer the question above, monitoring of the incidence of BEN in the early stage is more important. A recent study in the Kolubara River area has discovered new BEN or BEN-suspected cases and the authors consider that BEN is not tapering off [5]. However, early diagnosis of BEN is associated with the following unsolved questions on BEN—criteria for a correct diagnosis.

Criteria for diagnosis of BEN

The clinical diagnosis of BEN remains a problem because there is no single clinical or laboratory finding pathognomonic for BEN that differentiates it from other renal diseases. Therefore, the diagnosis is established only by ruling out other known renal diseases and searching for a sufficient number of criteria for the diagnosis of BEN. The most frequently used criteria are those proposed by Danilovic [6] which comprise the following: (i) farmers in the endangered villages, (ii) a familial history positive for BEN, (iii) mild proteinuria, (iv) low specific gravity of the urine, (v) anaemia, (vi) retention of nitrous compounds in the blood (urea >50 mg%, creatinine >1.5 mg%), and (vii) symmetrically shrunken kidneys. Using these criteria Danilovic suggested classification of patients in field studies into the group of suspected, cases who in addition to the first three, fulfil at least one of the
remaining three criteria, a group of affected patients who fulfil at least five out of six criteria.

Nevertheless, none of the suggested criteria is sufficiently specific. There are no studies evaluating sensitivity and specificity of these criteria. Except for the epidemiological criteria [1,2] most of the other studies refer to advanced stages of the disease [4–6]. Attempts to detect more sensitive and specific criteria for early diagnosis of the disease have not been successful so far. Studies of the diagnostic value of tubular disorders, particularly tubular proteinuria, have been performed [7,8]. Histopathological analysis makes the differential diagnosis of BEN significantly easier particularly in the early phase of the disease. Nevertheless, the morphological changes in BEN are non-specific and correspond to non-destructive, non-inflammatory renal diseases with marked changes of the blood vessels, impressive interstitial multifocal fibrous expansion and marked tubular atrophy, particularly of the outer cortex [9,10].

Specific and sensitive indicators of tubular lesions in BEN and evaluation of sensitivity and specificity of combinations of epidemiological, functional, and morphological criteria in the diagnosis of early stages of BEN should be the subject of future studies.

Kidney size—one of controversial morphological criteria

Symmetrical shrinkage of the kidneys is considered a criterion for the diagnosis of BEN [6]. Several groups of authors have pointed out that this shrinkage of the kidneys develops in the course of progression of renal failure; in the early, latent phase of the disease, the kidneys retain their normal size [10,11]. However, other authors suggest the shrinkage as an additional early and specific sign of BEN [12,13]. Some recent studies in which ultrason was applied for the measurements of the kidney size have also confirmed that patients with BEN and normal glomerular filtration rate have kidneys smaller than normal [3,14]. All this suggests that the criteria based on the size of the kidneys in the latent and initial stage of BEN have not been unified.

Kidney size and creatinine clearance

Recently we have presented an observation on the relation between creatinine clearance (Ccr) and kidney length [15]. Kidney lengths measured by ultrasonography in 84 BEN-suspected patients (39 males; 54±12.9 years) were compared with the values of 31 patients with other renal disease (15 males; 54±14 years; glomerulonephritis 13, pyelonephritis nine, nephrolithiasis four, obstructive nephropathy five). Only the patients with Ccr above 90 ml/min were included in the study.

The sonographic kidney length in all but one patient with renal disease other than BEN was less than 11 cm. Their Ccr varied between 90 and 177 ml/min; however, only three patients had Ccr above 150 ml/min. Out of 84 BEN-suspected patients, 38 had Ccr above 150 ml/min. The kidney length was 10 cm or less in 12 patients, 10.5 cm in seven and 11 cm or longer in the remaining patients. Comparing the kidney length of patients with Ccr above 120 ml/min from both groups, a significantly reduced mean kidney length was found in patients with BEN than in patients with other renal diseases.

In the population of so-called BEN-suspected patients, hyperfiltration, registered in majority patients, was associated with normal or small kidney size. Further investigation of the diagnostic and prognostic value of hyperfiltration as well as its pathogenesis would be warranted.

Conclusion

BEN was described in the second half of 1950s but many features of the disease have remained unelucidated. In the last decade the investigations of BEN slowed down due to well-known events in the region. Further investigations should be directed to investigation of the aetiopathogenesis, but also to
monitoring of BEN incidence in different endemic areas and to a better definition of criteria for diagnosis of the disease in the early, asymptomatic phase.

References


