Could Balkan Nephropathy be a Disorder of Renal Embryogenesis?

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Introduction

The etiology of Balkan endemic nephropathy (BEN) remains unknown despite numerous investigations carried out during the last 50 years. The pathophysiology of this disease remains unclear too, and there is no pathognomonic finding, which can confirm or discard the diagnosis of Balkan nephropathy in any particular patient. The widely accepted concept, however, is that Balkan nephropathy is a form of chronic tubulo-interstitial nephritis or some other form of chronic tubular injury to the kidney, which leads to tubular atrophy and severe reduction in kidney size (1). As such, Balkan nephropathy could be due to the action of any kind of toxic or infectious agent, including heavy metals, fungal toxins, radioactive substances, aromatic compounds, bacteria or viruses. However, after 50 years of research, no such factor has been yet identified with certainty enough to discard all other hypotheses and to define the etiology of this disease. Alternatively, Balkan nephropathy could be due to a genetic disorder, which leads to progressive tubular atrophy and renal failure. If this were the case and there were no environmental factor acting to produce the clinical manifestations of the disease, however, we would observe a steady incidence and prevalence over the years, and not the decline, which is now evident by looking back at the years passed. The most recent large population study, which was performed by Tz. Dimitrov and coworkers in the very last few years, discovered only 131 alive patients among a screened population of 3634 inhabitants of the 13 most endemic villages in Bulgaria (2). Three very important observations of this study deserve special attention: first, the number of alive patients has decreased with almost 90% in comparison with the number of patients registered during the late fifties and early sixties of the 20-th century; second, the mean age of the alive patients has increased markedly up to between 60 and 80 years of age, while virtually no patients under the age of 51 were registered; and third, interestingly, among the discovered patients, 87% were females, a very peculiar finding, which is in contrast with the almost equal sex distribution found during the BEN epidemic in the 1960-ies. Because the patient population grows older and decreases in number, it is obvious that there are no new young patients, but we only see the last survivors from a “wave” of affected patients, which had a maximum during the 1960-ies. Such observation cannot be attributed to a purely genetic disorder, without the action of an environmental factor, because a genetic disorder alone must produce a steady incidence and prevalence over many decades, as it is with the number of patients, for example, suffering from autosomal dominant polycystic kidney disease.

There are two types of events, which can cause a “wave” of new patients with kidney disease to emerge: one is any type of environmental factor, which might cause kidney damage in an adult subject, while the other is an environmental factor, which might have disturbed the renal embryogenesis and thus resulted in a “wave” of newborns, destined to develop slowly progressive renal failure during their adult life. The latter hypothesis has not been yet explored, and here we present evidence, which supports it:

Balkan nephropathy is a type of hypoplasia / dysplasia.

The severe reduction in kidney size, which is observed in patients with BEN, exceeds any other known renal disease causing renal failure and kidney atrophy. Kidneys as small as 5 cm in length have not infrequently been noticed in the advanced stages of the disease. Furthermore, reduced kidney size (to 10 or even 8 cm in length) has been discovered in many subjects even before any signs of kidney damage could be encountered (3). High prevalence (up to 60%) of renal artery aberrations has been discovered in a large cohort of patients with BEN, who were subjected to renal angiography by Tz. Dimitrov and coworkers during the years of the BEN epidemic (3). The most prevalent aberrations were short and very short renal arteries (shorter than 2 cm), as well as distorted and improperly divided renal arteries. In addition, high prevalence (8.5%) of duplicate calyx, duplicate ureter, horseshoe kidney and other similar aberrations of kidney development were discovered by J. Tanchev and coworkers in the Vratsa district hospital when reviewing all 1,960 X-ray renal imaging studies during the years of the epidemic (1962-1972) in this unscreened patient population (4). In 95% the malformations were unilateral, which suggests that intrauterine, but not genetic factors were the causes for renal malformations, because genetic causes generally lead to bilateral and uniform changes. In the latter report, less than 9% of the patients with kidney malformations were diagnosed as BEN patients, even though a very high prevalence of aberrations in kidney development was evident. Apparently, the lack of

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diagnostic criteria for BEN caused the patients with kidney aberrations not to be included in the whole picture of the observed epidemic. This, however, together with the reported high prevalence of renal artery aberrations, is the strongest argument favoring disturbed embryogenesis as the etiology of Balkan nephropathy. Furthermore, primitive glomeruli and ducts, which may be signs of renal dysplasia and hypoplasia, support the latter and have been described in biopsies of BEN patients (3). Finally, decreased number of renal lobes is characteristic for simple renal hypoplasia due to deficient branching morphogenesis during fetal growth and has also been described in BEN patients (3).

BEN is a type of a generalized proximal tubular acidosis (Fanconi syndrome)

This characteristic of the disease, although quite clear, does not appear to be widely recognized (5). While chronic tubulointerstitial nephritis typically causes distal tubular acidosis, patients with BEN have pure isolated tubular proteinuria (6), hypokalemia, glucosuria (very rarely reported) (7), aminoaciduria, and preserved ammoniagenesis in the early stages (8). By contrast, distal tubular damage is characterized by pronounced reduction in the ability to produce ammonia, which exceeds the degree of renal failure, and is frequently accompanied by nephrocalcinosis, the latter not being a feature of BEN. The syndrome of generalized proximal tubular dysfunction is accompanied by salt wasting and phosphate wasting. The former is the reason why hypertension is not a cardinal feature early in BEN, and why BEN patients exhibit slowly progressive renal damage. The latter may cause renal rickets, and may explain why BEN patients on dialysis do not exhibit hyperphosphatemia to the extent and severity, which is typical for other dialysis patients (9). There are more than 35 disorders, which can cause a proximal tubular disorder, and among those are a number of disorders of the renal development (10). We can only speculate about the exact nature of the impact on renal embryogenesis, which could have caused the epidemic of Balkan nephropathy in the early 20-ies of the 20-th century, but it could be related to the mass starvation during the Balkan wars, as well as to the great influenza epidemic, which struck a large human population during those years. Noteworthy, a genetic predisposition cannot be excluded as a factor, which may have determined the susceptibility to kidney damage, but still the greater amount of evidence favors the action of an environmental factor on renal embryogenesis as the major cause in the etiology of BEN.

References