WHAT DO WE KNOW ABOUT THE BALKAN ENDEMIC NEPHROPATHY AND THE UROEPITHELIAL TUMORS?

Momir Polenakovic¹, Vladisav Stefanović²

¹ Macedonian Academy of Sciences and Arts, Skopje, R. Macedonia
² Faculty of Medicine, University of Niš, Niš, Serbia

Corresponding Author: Polenakovic Momir, Macedonian Academy of Sciences and Arts, Bul. Krste Misirkov br. 2, 1000 Skopje, R. Macedonia; Tel: + 389 (0)2 3 23 54 00, Fax: + 389 (0)2 3 23 55 00, E-mail: maknelfpo@t-home.mk

Abstract

Balkan endemic nephropathy (BEN), a familial chronic tubulo interstitial disease with a slow progression to terminal renal failure, affects people living in the alluvial plains along the tributaries of the Danube River. One of its most peculiar characteristics is a strong association with upper urothelial cancer. An increased incidence of upper urinary tract (UUT) transitional cell cancer (TCC) was discovered among the inhabitants of endemic settlements and in families affected by BEN. In areas where BEN is endemic, the incidence of upper tract TCC is significantly higher, even 100 times, than in non-endemic regions. Until now, several hypotheses have been introduced about the etiopathogenesis of BEN. Only the toxic effect aristolochia clematidis has been confirmed as a factor in the occurrence of the disease. We don’t have specific biomarkers for an early diagnosis of BEN and UUT-TCC. With application of modern molecular and genetic methods in investigation of etiopathogenesis and diagnosis of BEN and UUT-TCC we should expect improvement in the study of BEN.

Key words: Balkan endemic nephropathy, upper urinary tract, transitional cell cancer.

Introduction

Balkan endemic nephropathy (BEN), a familial chronic tubulo interstitial disease with a slow progression to terminal renal failure, affects people living in the alluvial plains along the tributaries of the Danube River. One of its most peculiar characteristics is a strong association with upper urothelial cancer. An increased incidence of upper urinary tract (UUT) transitional cell cancer (TCC) was discovered among the inhabitants of endemic settlements and in families affected by BEN. In areas where BEN is endemic, the incidence of upper tract TCC is significantly higher, even 100 times, than in non-endemic regions [1, 2]. Until now, several hypotheses have been introduced about the etiopathogenesis of BEN. Only the toxic effect aristolochia clematidis has been confirmed as a factor in the occurrence of the disease. We would like to indicate several references that are of interest in the investigation of BEN UUT.

Some references about BEN – what do we know?!

• Polenaković M, Mojsiev B. Endemska nefropatija u selu Vitino (Kosmet) (Néphropathie endémique au village de Vitino (Kosmet)). Medicinski podmladak. 1962/63; XIV(4): 363–71.


What do we know about the Balkan endemic…


Do we have molecular markers for BEN – PROTEOMICS? The requirements for molecular markers are:
- High sensitivity and high specificity.
- Increased capability of diagnosis of tumors in primary stage, mainly in situ cancers.
- To be independent of subjective factors like methodology and examiner’s experience.
- To be a method with reproducible results.
- To be a quick, simple and easy method.
- To be with the least possible discomfort for the patient.
- To provide results at a low cost.

Further studies in the urothelial cancer suggest:
- Identify the involvement of genes which are either novel or have previously not been known to be involved in the development of early stage TCC.
- Identify genes predisposing to BEN.
- Identify genes predisposing to TCC associated with BEN.
- Identify biomarkers for detection of predisposition to TCC before the clinical manifestation of the disease.
• Provide information on the combine molecular signatures (of gene and gene products—mRNA; protein) of pTa/pT1 TCC – this complex approach has a higher sensitivity for detection of diagnostic and prognostic biomarkers for high and low risk groups of tumors than the separate high throughput study.
• Determine the significant changes in gene/protein expression between early stage TCC with and without progression.
• Identify urine proteomics markers for monitoring the disease.
• Identify biomarkers for invasive TCC.
• Identify predictive biomarkers for chemosensitivity of TCC.

We should examine more the epigenetics factors and in general, the influence of environment to genotype and phenotype of the disease.

Several questions are enumerated for further collaborative studies, to give answers:
• Do we know current topographical distribution of BEN?
• Would genetic research solve the problem of BEN etiology?
• How to direct collaborative etiological studies?
• Is the exposure to the unknown BEN agent currently going on?
• How to assess it?
• Which tests should be used to pick up possibly affected individuals in a screening of BEN?
• Is mass screening of BEN ethically justified?
• Should the population be mass screened for UUT?
• How to identify cases outside of BEN foci?
• How to make BEN research more methodologically sound?

Prevention and treatment of ben
We just started to unravel the etiology of BEN and associated urothelial cancer.

Since BEN was first described, around half a century ago, socioeconomic changes (in housing, farming, living standards, etc.) have been profound and the effect of environmental toxicants has been reduced. Genetically susceptible persons have become ill and have died.

Avoidance of etiological factors is the best prevention.

As aristolochic acid is the probable toxicant in the South Morava region, in Croatia and in Bulgaria, the number of BEN and associated UUT has been reduced and probably will disappear.

Treatment of BEN is similar to that of all chronic interstitial nephropathies. Patients with BEN should pay close attention to cardiovascular risk and stop smoking, eat healthy and balanced diet, and take regular exercise.

Hypertension should be treated with ACEIs and ARBs. A low protein diet can be used in CKD stages 3 and 4.

Hemo- and peritoneal dialysis as well as kidney transplantation have been used with success. BEN does not recur after renal transplantation.

With longer survival on renal replacement therapy, patients develop tumors of the renal pelvis, ureter, and urinary bladder. And long term surveillance is required for that. Pretransplant bilateral uretero-nephrectomy is necessary to prevent urothelial cancer on native urinary tract [3, 4].

There are more questions than answers in the investigation of BEN. So, we expect fruitful results from this meeting about BEN.

REFERENCES
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