ISSN 0350-1914
UDC: 616.61-036.21(497)

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

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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.

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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.

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Р е з и м е

ШТО ЗНАЕМЕ ЗА БАЛКАНСКАТА ЕНДЕМСКА НЕФРОПАТИЈА И ЗА УРОЕПИТЕЛИЈАЛНИТЕ ТУМОРИ?

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Балканската ендемска нефропатија (БЕН) е фамилијарна хронична тубулоинтерстицијална болест со бавно напредување до терминална бубрежна инсуфициенција, ги зафаќа луѓето кои живеат во алувијалните рамнини по должина на притоките на реката Дунав. Една од нејзините најзначајни карактеристики е силна поврзаност со карцином на горниот уротелиум. Зголемена инциденца на карцином на преодни клетки (ТСС) на горниот уротелиум била откриена меѓу жителите на ендемични населби и кај семејствата погодени од БЕН. Во областите каде што БЕН е ендемска, инциденцата на ТСС во горниот тракт е значително повисока, дури и 100 пати отколку во неендемските региони. Досега, неколку хипотези се дадени за етиопатогенезата на БЕН. Само токсичниот ефект на Aristolochia clematidis е потврден како фактор во појавата на болеста. Немаме специфични биомаркери за рана дијагноза на БЕН и на карцином на горниот уротелиум – ТСС. Со примена на современи молекуларни и генетски методи во истражувањето на етиопатогенезата и дијагнозата на БЕН и карцином на горниот уротелиум – ТСС се очекува подобрување во истражувањето на БЕН.

Клучни зборови: балканска ендемска нефропатија, горен уринарен тракт, карцином на преодни клетки.