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BALKAN ENDEMIC NEPHROPATHY – ALL DILEMMAS ARE SOLVED?

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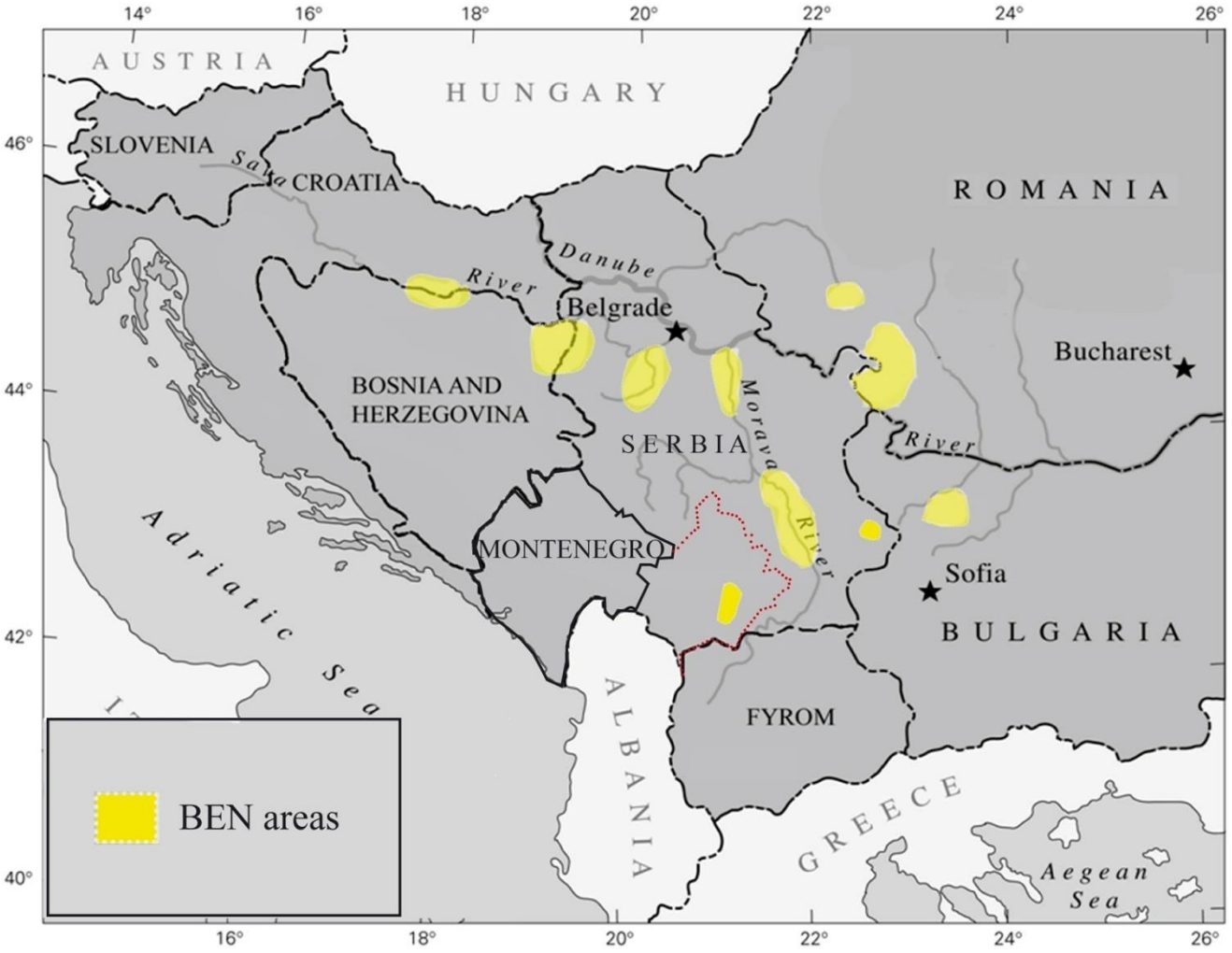
BALKAN ENDEMIC NEPHROPATHY (BEN)

1. BEN, originally described in 1956, is a unique familial, chronic renal disease encountered with a high prevalence rate in, Bosnia and Herzegovina, Bulgaria, Croatia, Romania, and Serbia

2. The first cases were described in:

- Bulgaria: Tanchev Y, et al. Studies on the nephritides in the District of Vratza. *Savremena Medicina* 1956; 7: 14-29
- Serbia: Danilovic V, et al. Chronic nephritis due to lead poisoning by digestive route (flour). *Presse Med* 1957; 65: 2039-2040 (in French)
- Romania: Fortza N, et al. Nefrita cronica azotemia endo-epidemica. *Stud Cercet Med* 1961; 1: 217-221

Geographical distribution of BEN



Epidemiology

1. There are no clear-cut data on the current trend for the incidence and prevalence of BEN
2. The studies carried out in different endemic areas have produced conflicting information
3. Some epidemiological studies reported
   - An increase in the prevalence of BEN between 1967 and 1970
   - A steady state between 1970 and 1984 and
   - Ultimately a decrease in some endemic areas
   - Similarly, in another endemic area, a decreasing incidence over time was found during a follow-up period from 1978 to 1997

Epidemiology

1. Assessments are frequently based on the number of BEN patients on dialysis
2. In Serbia, BEN patients represent an average of 6.5% (5–46%) of the dialysis population
3. Estimations: almost 100 000 people are at risk, 25 000 have BEN
4. Despite intermittent variations, the incidence remained stable over time.
5. Differences may be related to
    - Changes in the study design
    - True epidemiological differences between sequential time frames and BEN areas
    - Consequence of the natural course of the disease

BALKAN ENDEMIC NEPHROPATHY (BEN)

The main features of the disease are:

- Endemic nature
- Long incubation period
- Familial clustering of the disease, and
- Unusually high incidence of associated upper urothelial cancers (UUC)

Clinical signs and symptoms

Non-specific and often remain unrecognized for years

The initial asymptomatic period is followed by:

- Weakness and lassitude,
- Mild lumbar pain,
- Pallor of the skin and
- Copper brownish discoloration of the palms and soles

Blood pressure is usually normal

Anaemia

Intermittent proteinuria

Sparse urinary sediment

Loss of urine concentration capacity

Very small contracted kidneys

Diagnostic criteria

There are no pathognomonic diagnostic features of BEN

The set of:

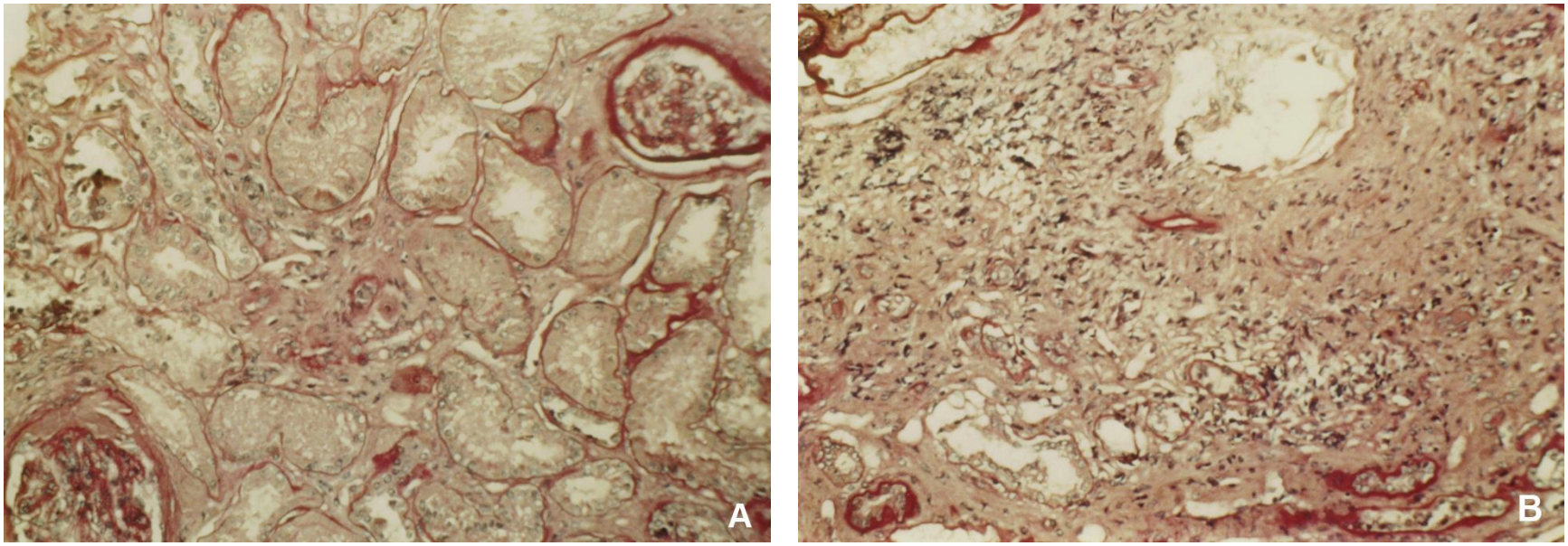
- Epidemiologic
- Clinical and biochemical data
- Pattern of pathologic injury
- Absence of any other renal diseases
- Familial clustering of the disease

Are highly suggestive of this entity

Pathology of BEN

The pathology of BEN is characterized by a progressive atrophy and sclerosis of all structures of the kidney, and it shares similarities with tubulointerstitial kidney diseases

Pathology of BEN



A - Advanced glomerular sclerosis (initial obsolescence), with interstitial sclerosis and tubular atrophy (PAS, x250).

B - Focal tubular atrophy with prominent interstitial sclerosis and clearly delineated mononuclear infiltrate (PAS, x250)

Čukuranović R. Genetic and morphophysiologic study of Balkan endemic nephropathy. Doctoral Thesis. Medical Faculty, University of Niš, 1-169, 1992 (in Serbian)

All hypotheses related to BEN can be classified into three main groups

A. Exogenous factors

- (a) Lead intoxication
- (b) Selenium deficiency
- (c) Intoxication with Aristolochia Clematitis
- (d) Ochratoxin A
- (e) Pliocene lignite

B. Endogenous factors

- (a) Genetic predisposition
- (b) Changes in enzyme activity;
  - LCAT deficiency
  - Decreased erythrocyte ALA-D activity
  - Changes of CYP2D6 activity
- (c) Genetic polymorphism
- (d) Chromosomal aberrations
- (e) Viral disease

C. Miscellaneous factors - Multifactor

Lecithin cholesterol acyltransferase (LCAT) - Organic substances from coal

CHN = AAN = BEN

Although the aetiology has been extensively studied, fostering the publication of various hypotheses, only one of them has provided conclusive evidence related to the aetiology of BEN.

Studies conducted over the past decade have provided particularly strong arguments that BEN and UUC are caused by chronic poisining with Aristolochic acids (AAs)

CHN = AAN = BEN

1. In 1969, Ivić proposed that the aetiology of BEN could be related to chronic A. clematitis poisoning in which seeds from these plants intermingle with wheat grain during the harvesting process

2. He speculated that human exposure to a toxic component of Aristolochia might occur through ingestion of bread prepared from flour derived from contaminated grain.

3. These well-documented results attracted more interest from the scientific community many years later

Aristolochia clematitis

(A) A. clematitis growing in the wheat field

(B) Post harvests second generation A. Clematitis

(C) Ripe seeds in the soil

(D) Wheat grain from that field

Hyper endemic village Petka, Serbia, 2011

CHN = AAN = BEN

1. In 1990, a clinic in Brussels began prescribing capsules as part of a slimming regimen consisting of Chinese herbal remedies believed to contain in part, Stephania tetrandra (in Mandarin Han Fang-Ji)

2. Unintentionally, it was replaced by Aristolochia fangchi (Guang Fang-Ji in Mandarin) since both plants are used in Chinese traditional medicine carrying similar names (Fang-Ji)

3. CHN reported in Belgium in 1993 presented as a rapidly progressive renal interstitial fibrosis leading to end-stage renal disease

4. It emerged that almost half of the CHN patients developed UUC.

CHN = AAN = BEN

1. Exposure of CHN patients to AA that belongs to the family of carcinogenic, mutagenic and nephrotoxic compounds was substantiated by the identification of AA-DNA adducts

2. Once established, AA–DNA adducts persist for years in the renal cortex, serving as reliable biomarkers of exposure to AA

3. The outbreaks of AA-associated renal failure have been subsequently reported in several other countries, and the name was replaced by Aristolochic acid nephropathy (AAN)

CHN = AAN = BEN

1. Cosyns first raised awareness to the unique renal histopathology of CHN with its striking similarity to BEN

2. The similarities between CHN and BEN have led to the hypothesis of a common aetiological agent for both diseases. This hypothesis implies that:

a. BEN, CHN and AAN are the same disease
b. Dietary ingestion of AA, in conjunction with individual genetic susceptibility, accounts for all-epidemiological, clinical, and pathophysiologic features of BEN and associated UUC

CHN = AAN = BEN

A recent publication presented results showing:

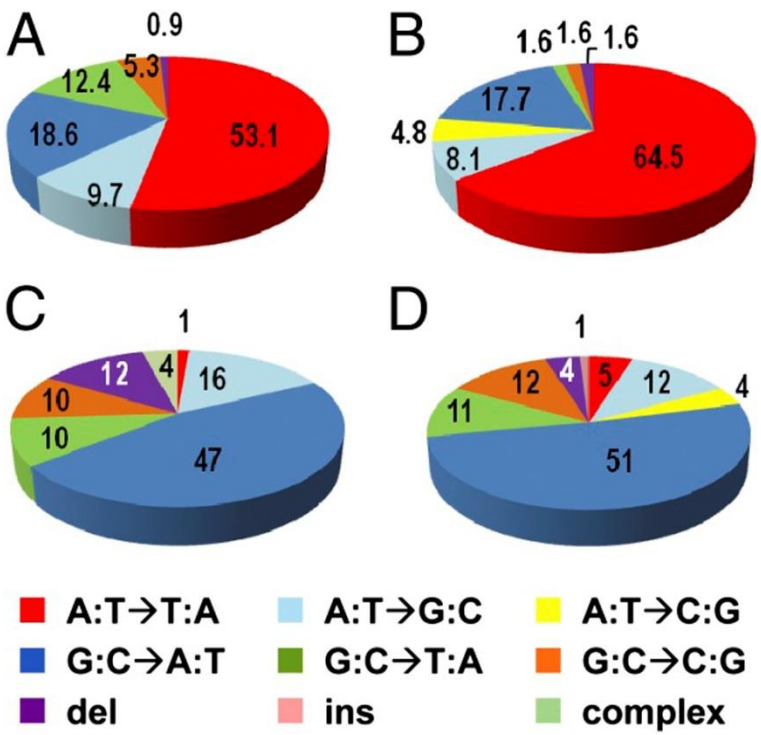
- That the accumulation of AA-DNA adducts was present in the renal cortex and UUT of five patients with BEN from an endemic region in Croatia
- But not in five patients with other forms of CKD or five patients with UUC living in a non-endemic area of Croatia
- The finding by Grollman et al. of AA-derived DNA adducts in renal cortical and urothelial tumor tissue of patients with documented BEN, *Association with the dominance of the A:T → T:A transversions in the TP53 tumor suppressor gene mutational spectrum was a breakthrough in the identification of AA as an aetiological agent of the UUC observed in BEN

CHN = AAN = BEN

Unique features of this spectrum, including the predominance of A:T→ T:A transversions found also in Taiwanese patients with UUC confirmed the hypothesis that:

- All components of the AA signature TP53 mutational spectrum, established in the context of UUC associated with BEN, are similarly found in Taiwanese patients with UUC

CHN = AAN = BEN



TP53 mutational spectra in urothelial carcinomas:

A - TP53 mutations in DNA obtained from UUC in endemic regions of Bosnia, Croatia and Serbia (62 mutations);

B - TP53 mutations in DNA obtained from UUC in Taiwan (113 mutations).

C - TP53 mutations in urothelial carcinomas of the renal pelvis and ureter, worldwide (73 mutations).

D - TP53 mutations in urothelial carcinomas of the renal pelvis, ureter, bladder, and nonspecified urinary organs, worldwide (696 mutations).

Chen CH, Dickman KG, Moriya M, et al. Aristolochic acid-associated urothelial cancer in Taiwan. Proc Natl Acad Sci USA 2012; 109: 8241-8246)

- Comparison of methylation profiles of BEN patients and corresponding controls revealed differently methylated regions.

- This suggests that dysregulation of genes involved in immunological response could be a common mechanism in BEN pathogenesis of both genders.

Staneva R, et al. Whole genome methylation array analysis reveals new aspects in Balkan endemic nephropathy etiology. *BMC Nephrol*; 2013;14:225

- The frequency of all annotated genetic variants with deleterious/damaging effect was compared with those of European populations.

- No statistically significant difference between annotated variants in BEN patients and European populations were found.

Toncheva D, et all. NGS nominated CELA1, HSPG2, and KCNK5 as candidate genes for predisposition to Balkan endemic nephropathy. *Biomed Res Int*; 2014;2014:920723

- Mutant genes (CELA1, HSPG2, and KCNK5) in BEN patients encode proteins involved in basement membrane / extracellular matrix and vascular tone, are tightly connected to process of angiogenesis.

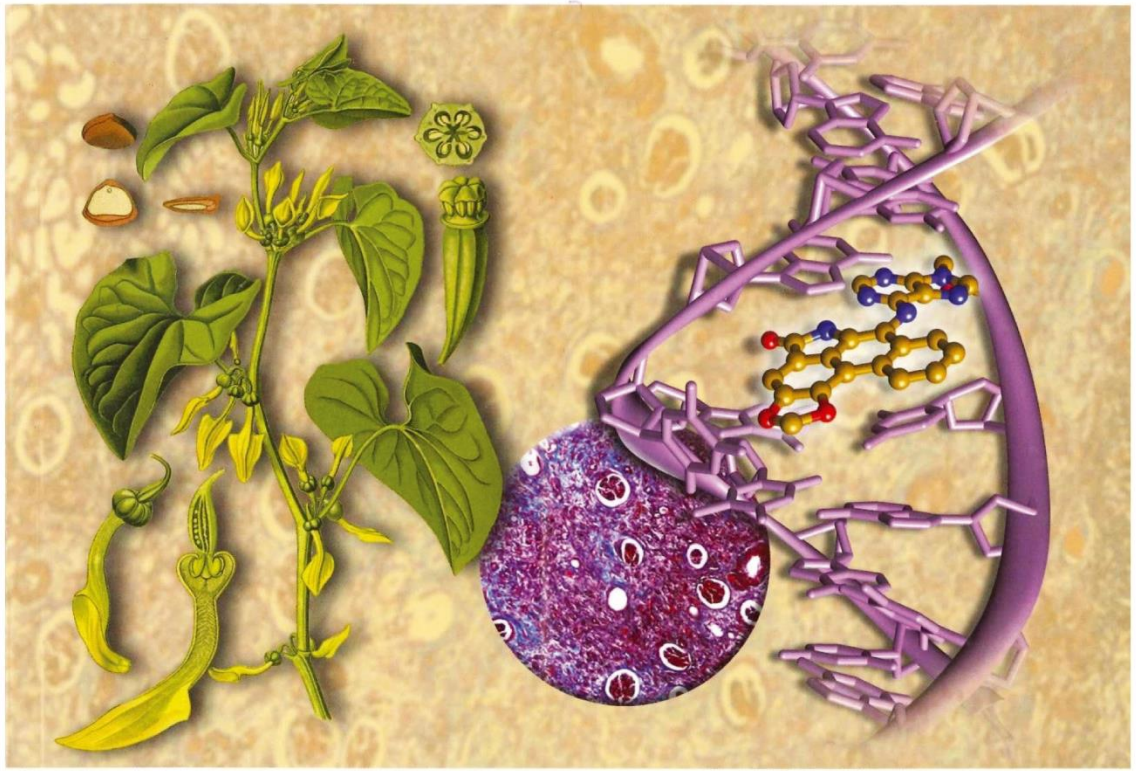
- We suggest that an abnormal process of angiogenesis plays a key role in the molecular pathogenesis of BEN.

Toncheva D, et all. NGS nominated CELA1, HSPG2, and KCNK5 as candidate genes for predisposition to Balkan endemic nephropathy. *Biomed Res Int*; 2014;2014:920723

Conclusions

- In light of the persistent widespread use of Aristolochia herbal remedies in traditional Chinese medicine and recently published data that some crops can take up AA from the soil, one can accept that AA could be responsible for a previously and currently widespread unrecognized global renal disease and UUC
- It is now clear that BEN represents a form of AAN, from which it is pathologically indistinguishable and we can with highest confidence apply the equation: CHN=AAN=BEN
- Prevention of exposure to AA is a key public health priority
- Prevention of exposure to AA in parts of the Balkans where BEN is prevalent, and elsewhere has not received sufficient attention since establishment of the etiologic relationship between AA and the disease

kidney
INTERNATIONAL



Volume 81 Issue 6 MARCH (2) 2012

AP Grollman et al

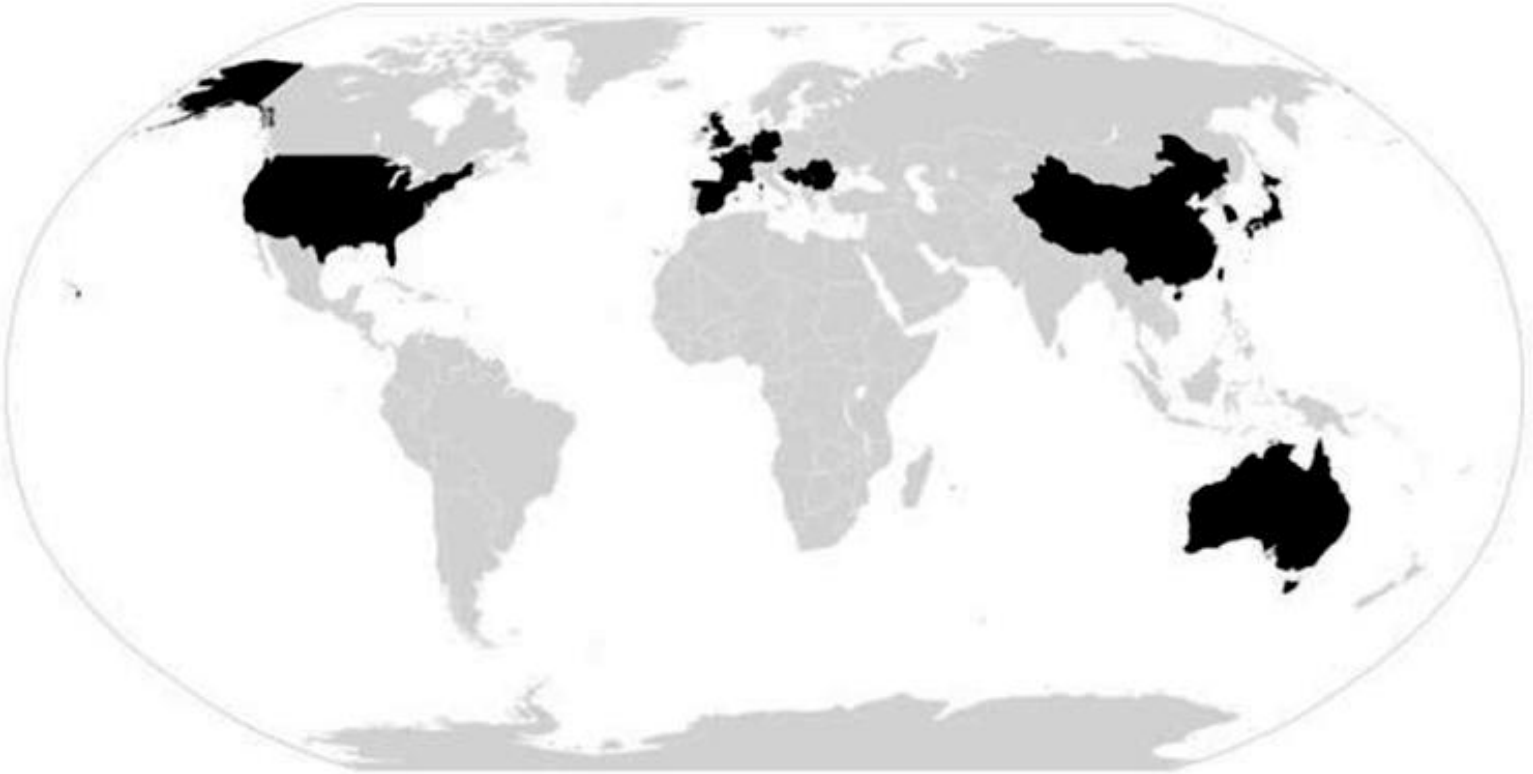
M.E. DeBroe (commentary)
Chinese herbs nephropathy and Balkan endemic nephropathy: toward a single entity, aristolochic acid nephropathy
Kid Int (2012) 81, 513-515

Conclusions

- There is an urgent need for research addressing many key areas:

  a. Determining the true worldwide extent of exposure
  b. Defining of genetic variants that might be responsible for increased sensitivity or resistance to the nephrotoxic effects of AA
  c. Testing the accuracy and usefulness of diagnostic criteria and finding the optimal screening protocols
  d. Developing therapeutic agents that can reverse or delay progression of the disease.

World map showing the epidemiology of AAN or BEN

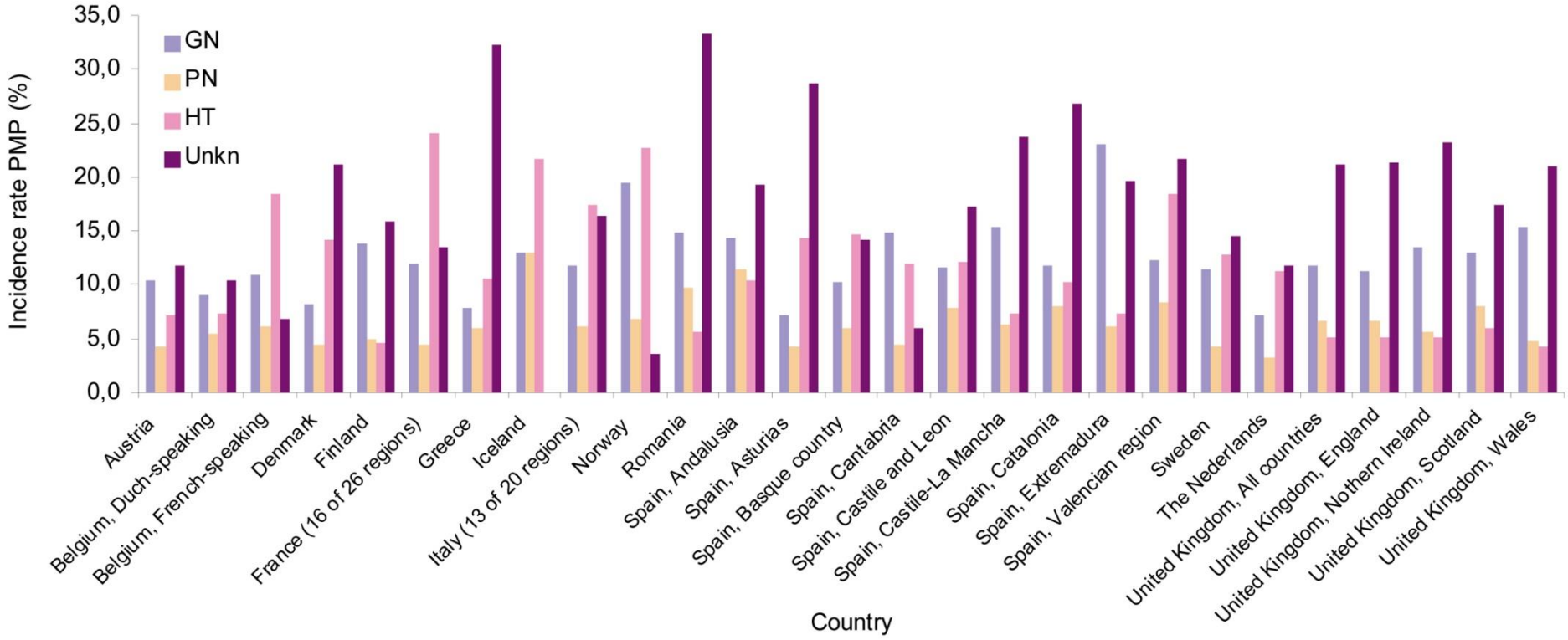


Countries in which cases of AAN or BEN have been reported in the literature are highlighted. It is likely that the true worldwide distribution of the diseases extends beyond the countries highlighted, especially in the Far East and South Asia.

Gökmen MR, Cosyns JP, Arlt VM, et al. The epidemiology, diagnosis, and management of aristolochic Acid nephropathy: a narrative review. Ann Intern Med. 2013; 158(6): 469–477.

Incident rates per million population, unadjusted

at day 1, by cause of renal failure



EUROPEAN RENAL ASSOCIATION ERA-EDTA Registry. Annual Report 2008.

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