DOI: 10.2478/10004-1254-59-2008-1865

Review

MYCOTOXIC AND ARISTOLOCHIC ACID THEORIES OF THE DEVELOPMENT OF ENDEMIC NEPHROPATHY

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Received in November 2007
Accepted in January 2008

Despite many efforts of scientists and epidemiologists, the aetiology of endemic nephropathy (EN) is still unknown. This disease occurs in the rural population of geographically limited areas of Bulgaria, Bosnia and Herzegovina, Croatia, Romania, and Serbia, and a number of theories have been proposed about its aetiology. The mycotoxin theory has prevailed until now, based on the studies of nephrotoxic mycotoxin ochratoxin A (OTA) that revealed higher frequency of OTA-positive food and blood samples in endemic than in non-endemic areas.

However, a new aristolochic acid (AA) theory of EN origin has been proposed recently, due to the histological similarities in kidney lesions between patients suffering from EN and patients suffering from Chinese herbs nephropathy caused by AA. Until now it has not been unequivocally proved that the inhabitants of EN areas are exposed to higher concentration of AA than in other regions and the exposure pathways are rather uncertain.

This paper presents most important studies supporting both theories, indicating also the inconsistencies of each.

KEY WORDS: *Chinese herbs nephropathy, DNA adducts, kidney tumours, mycotoxins, ochratoxin A, p53*

Endemic nephropathy (EN) is a bilateral chronic kidney disease that occurs in the rural population of some areas of Bulgaria, Bosnia and Herzegovina, Croatia, Romania, and Serbia. This fatal disease is characterised by focused and limited geographical distribution, occurrence in farming households, and high mortality from uraemia. It is interesting that since the disease was discovered, the endemic areas are stable; there are no new endemic areas, and none of them has become non-endemic. There are no cases of EN in towns, although they are close to endemic villages. The first outbreak of the disease in the endemic areas of all affected countries occurred simultaneously in the early 1950s, although there are indications that sporadic cases were seen earlier. Ten years later, a high incidence of otherwise rare urothelial tumours was recorded, first in the endemic area of Bulgaria, and then of other countries. Although a number of more or less plausible hypotheses have been proposed, the origin of EN is still unknown.

The mycotoxin theory of the development of EN was postulated in the early 1970s, because of similar kidney lesions in pigs exposed to mycotoxin ochratoxin A (OTA) and humans suffering from EN. A number of field studies were performed, mostly in Bulgaria and Croatia, whose aim was to confirm or reject this theory.

In 1992 a number of cases of interstitial nephritis were recorded in young women in Belgium, and later in other European countries that were followed

by end-stage renal disease (1). All patients followed the same slimming regimen with Chinese herbs that accidentally contained *Aristolochia fangchi*, a herb with a known nephrotoxic compound, aristolochic acid (AA) which causes the so called AA nephropathy (AAN). Histopathological similarities between kidney lesions in EN and AAN have recently resuscitated the old theory of the involvement of AA in EN.

This paper reviews the main research findings supporting or opposing either the OTA or AA theory of EN origin.

EPIDEMIOLOGICAL FEATURES OF ENDEMIC NEPHROPATHY AND CHINESE HERBS NEPHROPATHY

From the early 1950s when EN was recognised as a nosologic entity, its appearance in Croatia changed significantly. In 1957-1960 the average age of patients at death was 45.1 years, while in 1991-2002 it was 69.2 years (2, 3). Although this increased life expectancy, similar to that of the general population in the area, is probably owed to lower exposure to the toxic compound, there are still new cases of the disease, and it does not disappear (4).

EN occurs exclusively in rural population, even though the endemic areas are located near towns. It still has not been proved that chronic interstitial nephropathies of unknown aetiology seen in North Africa (Egypt and Tunis) are OTA-caused EN (5-7), because high concentrations of OTA may also be found in patients with severe kidney failure (8). Therefore, it seems that EN neither expands nor disappears from the endemic areas (9). This is opposite to AAN, which appeared as an epidemic in the urban population first in Belgium in 1991 and then in other European countries, and the USA (10, 12). The other difference is that EN is the disease of familial or environmental clustering, while AAN is not. The sex ratio in EN is approximately 1:1, while AAN is dominant in women because women attended slimming clinics (10).

It also seems that exposure duration is quite different between EN and AAN. EN does not occur in children, but the inhabitants that have left the endemic area after over a decade of residence there are also known to develop EN. Patients with AAN usually developed the disease after several years of treatment with Chinese herbs (10, 11). In some cases nephropathy was characterised by a rapid deterioration in renal function, with initial serum creatinine doubling within about three months.

The development of urinary tract malignancy is also much slower in EN than in AAN. In the Croatian endemic area, the appearance of carcinomas of the urinary system peaked ten years after the peak of endemic nephropathy (2). In another endemic area, the latency for malignancies ranged between 20 and 27 years, while in AAN urothelial tumours occurred within two to six years (13, 14).

EXPOSURE TO OCHRATOXIN A AND ARISTOLOCHIC ACID IN THE ENDEMIC AREAS

Due to the endemic character of EN and its exclusive occurrence in rural population, it is believed that the causative agent of EN should be a natural nephrotoxic and carcinogenic compound more frequently found in the endemic than in non-endemic areas. The long latency of EN in persons who had lived in the endemic areas for at least 10 years and moved, suggests that the causative agent is slow-acting and that exposure continued for many years.

Mycotoxin OTA is a natural compound with nephrotoxic and carcinogenic properties, and was extensively investigated as the possible cause of EN. This product of moulds from the genera *Aspergillus and Penicillium* was found in the food and feed in the endemic areas (15). In humans, OTA was first detected in the blood of residents of the Croatian endemic area (16). A ten-year follow-up of OTA blood concentrations showed that these residents were more frequently exposed to OTA than controls (17). This study was performed on samples collected in winter, but later studies showed that OTA exposure is the highest in the summer, which means that this ten-year follow up did not measure the peak exposure (18). In Bulgaria, 576 blood samples were collected in the endemic and non-endemic areas in 1984, 1986, 1989, and 1990. OTA was detected in all groups, but was more frequent in patients with EN and urinary tract tumours than in healthy subjects in the endemic and control areas (19). According to studies referred to here, residents of the endemic areas are more frequently exposed to OTA than other populations, but because of the high variability in OTA concentrations, mean blood OTA in patients with EN was not significantly

higher than in controls. OTA has demonstrated its nephrotoxic properties in all laboratory animals, and there is no reason that it should not have the same effects in humans. OTA was found in food and feed all over the world (20), and low OTA concentrations were found in residents of countries where EN has not been identified so far (21). However, this finding does not discard mycotoxins as possible causes of EN, because there are other mycotoxins (such as citrinin, penicillic acid, and fumonisins) with nephrotoxic properties that may have a synergistic effect (22-26).

According to the AA theory, residents of the endemic areas suffering from EN are exposed to aristolochic acid from the seeds of *Aristolochia clematitis* (birthwort) contaminating the wheat. However, this exposure seems rather uncertain. The only paper dealing with this problem analysed a questionnaire about the presence of birthwort in the fields. Patients with verified EN remembered more frequently than healthy individuals that their fields were severely infested with birthwort (27). Both controls and EN patients declared that birthwort disappeared from their fields with more consistent use of herbicides and drainage that decreased humidity needed by the plant to grow. The authors did not mention that possible wheat contamination with birthwort 20 to 30 years ago does not entail higher exposure to AA, because at that time the usual practice was that farmers brought sacks of wheat to the mill where they immediately exchanged them for sacks of flour from wheat produced by other farmers. In other words, it is hard to establish real exposure to AA. Furthermore, birthwort is ubiquitous in Croatia, and there is no explanation why it should cause severe lesions only in the endemic area. Other authors also raised similar doubts. Thus, Long and Voice (28) say that in an EN area wheat is typically harvested in mid-summer when birthwort seeds are immature and contained within a large bulb that can easily be separated from the wheat grain. They also claim that combine harvesters have been used in some villages for many years and that these would easily screen off immature bulbs. For long many villages have had modern mills with sophisticated separation technologies. There is no evidence that bread is contaminated, or that AA exposure is consistent with the occurrence of EN (29). It should be stressed that so far no food analysis has demonstrated the presence of AA in food of the residents of the endemic areas.

CLINICAL PICTURE OF EN AND AAN

Since the early description of EN given by Radonić et al. (30), the clinical picture of this disease has not changed. EN is still a slow-progressing nephropathy of tubular type with the insidious onset. The initial appearance of interstitial fibrosis without affecting the glomerules and clinical presentation of mild hypertension is rather similar between EN and AAN. EN appears after non-specific signs such as fatigue, headache, loss of body weight, and pale skin. The effect on the tubules is characterized by a decrease in tubular transport that manifests itself in a very mild intermittent proteinuria and gradual rise of blood nitrogen (31). Mild anaemia either of aplastic or normochromic type is an early sign of EN, but blood pressure increases significantly only with greater impairment of the kidney function.

The main dermatological features of EN are yellow discoloration and dark stained palm lines that are not seen in AAN. In AAN anaemia is severe from the very beginning, and renal impairment may be slowed by steroid treatment (32).

It takes decades for EN to progress from the non-symptomatic phase to the end-stage renal disease, while in AAN this progression is much faster (a few months or years) (14, 31). The other difference in clinical picture is that ureterohydronephrosis has not been reported in EN except in cases of urothelial tumors, while it is frequent in AAN (14). The single pathological difference between the two diseases lies in the more extensive and constant involvement of the columns of Bertin in AAN than in EN (1).

OTA-DNA, AA-DNA ADDUCTS AND p53 MUTATIONS IN EN AND AAN

It is well known that OTA and AA are carcinogenic in laboratory animals. Chemical carcinogens or their reactive metabolites bind covalently to the DNA molecule, forming thus DNA adducts. However, the presence of DNA adducts does not necessarily prove the involvement of a compound or its metabolite in the aetiology of cancer, but it does evidence exposure. OTA-DNA and AA-DNA adducts were found in the liver and kidney of experimental animals after respective OTA and AA treatment using the ^{32}P-postlabelling method (33-35). Some authors have raised doubts about the origin of OTA-DNA adducts, suggesting

that OTA and its metabolites can not form covalent bonds with DNA, and that adducts seen in the tissues of OTA-treated animals are the products of OTA-mediated cytotoxicity (36, 37).

In several studies, these adducts were detected either simultaneously or separately in human kidney or in tumour tissues of the urinary tract. In a preliminary study of OTA-DNA and AA-DNA adducts in the kidney tissue of three Croatian patients with EN, both types of DNA adducts were found simultaneously in two samples, while no adducts were found in one (38).

OTA-DNA adducts were also found in eight tumour tissues of the kidney and urinary bladder of Bulgarian subjects that lived in a high-risk area for Balkan endemic nephropathy (39). In contrast, OTA-DNA adducts were not found in the tumour kidney tissues of French patients with AAN, analysed as controls. Instead, these and the tissues of surgically removed kidney, urothelial or tumor tissues of patients with AAN in Belgium contained only AA-DNA adducts (40). In a recently published paper OTA- and citrinin-DNA adducts were detected in the tumour kidney tissues of patients with EN from Croatia, Bulgaria, and Serbia, but AA-DNA adducts were not (41).

In contrast, there are authors reporting the presence of AA-DNA adducts in four renal cortex samples in patients with EN and in three upper urinary tract tumour samples in patients from the endemic area of Croatia (42). These samples were not checked for the presence of OTA-DNA adducts.

Carcinogenesis is believed to be genetically determined and a consequence of the disrupted function of tumour suppressor genes or of the activation of oncogenes. The most studied mutations are changes in the p53 suppressor gene.

An analysis of p53 mutations revealed a statistically significant difference between mutation spectra in both the kidney and liver of AA-treated and control rats (34). In the liver and kidneys of AA-treated rats the predominant mutation was A:T→T:A transversion, whereas the main type of mutation in controls was G:C→A:T transition. Mutation A:T→T:A was found also in urothelial tumor cells of one patient with AAN (43). In 11 samples of transitional cell carcinomas in residents of endemic villages, 19 base substitutions were identified (42). All but one patient had at least one A:T→T:A mutation, and this mutation accounted for 78% of all base substitutions detected. This high a percentage of p53 mutations was not found in a study of 90 blood samples of Bulgarian patients with EN; they were found in 10 % of samples (44).

CONCLUSIONS

EN is a disease that occurs endemically in rural population, which indicates that a natural toxin should be involved in the aetiology of this disease. OTA and AA have nephrotoxic and carcinogen properties, and exposure to either of them may cause severe kidney lesions and tumours of the urothelial system. Until now, exposure to AA has been associated with the slimming regimen in young women in many highly developed countries, while EN has been the disease of the elderly rural population of both sexes. This suggests that the involvement of AA in the development of EN is not likely, which has also been concluded by Pfohl-Leszkowicz et al. (41).

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Sažetak

MIKOTOKSINSKA I ARISTOLOHIČNA TEORIJA O UZROKU ENDEMSKE NEFROPATIJE

Unatoč mnogim nastojanjima znanstvenika i epidemiologa, etiologija endemske nefropatije (EN) još nije razjašnjena. Postavljeno je više teorija o nastanku ove bolesti koja se javlja u ruralnom stanovništvu na geografski ograničenim područjima Bugarske, Bosne i Hercegovine, Hrvatske, Rumunjske i Srbije. Donedavno se najviše napora ulagalo u istraživanje povezanosti nastanka EN s izloženošću mikotoksinu okratoksinu A. Prikupljeni rezultati upućuju većim dijelom na opravdanost te pretpostavke. Zbog histoloških sličnosti bolesnika s EN i pacijentica koje boluju od nefropatije uzrokovane kineskim travama za koju je ustanovljeno da ju uzrokuje aristolohična kiselina (AA) postavljena je teorija da je AA uzročnik EN. Dosad nije potvrđeno da su stanovnici na lokalizacijama s endemskom nefropatijom izloženi povišenim koncentracijama AA u usporedbi s područjima bez te bolesti. Osim toga su i putovi izloženosti AA koji bi se mogli povezati s pojavom EN nejasni i nedokazani.
U ovom preglednom radu izneseni su rezultati najvažnijih istraživanja koja podupiru ili negiraju obje teorije, zajedno s nedostatcima svake od njih.

KLJUČNE RIJEČI: *DNA-adukti, mikotoksini, nefropatija kineskih trava, okratoksin A, p53, tumori bubrega*

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