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ANALGESIC NEPHROPATHY, BALKAN ENDEMIC NEPHROPATHY AND CHINESE HERBS NEPHROPATHY: SEPARATE TUBULOINTERSTITIAL KIDNEY DISEASES ASSOCIATED WITH UROTHELIAL MALIGNANCY

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Summary. *Analgesic nephropathy (AN) was described in 1953 as tubulointerstitial kidney disease associated with chronic abuse of analgetic mixtures. Chinese herbs nephropathy (CHN), another tubulointerstitial kidney disease, on the basis of morphological and clinical grounds, was found similar to Balkan endemic nephropathy (BEN), and a common etiologic agent, aristolochic acid, was suspected. However, several different features of BEN, AN and CHN are demonstrated. Progression to end stage renal disease is much faster in CHN than in AN and BEN. In CHN the fibrotic process is not confined to kidneys only but was extended to renal pelvis and ureter, peritoneal membrane and aortic valve. Kidney atrophy in BEN is symmetric with a smooth outline; in CHN kidneys are asymmetric in 54%, with irregular outline. In CHN extensive fibrosis develops with marked tubular atrophy and disappearance of atrophic tubules. Kidney papillary necrosis is the landmark of AN.*

Classical AN appears to be markedly less common than 20 years ago. Reduction in exposure to phenacetin and combination preparations, however, has not eliminated AN. The exact prevalence of this disease in various countries all over the world is still unclear fifty years after the original description of this entity. The magnitude of analgesic exposure-related renal disease today is unclear both as a primary cause of disease and as a cofactor of renal disease of known etiology. National studies to evaluate the prevalence of AN among incident ESRD patients, leading to national programs to combat this preventable kidney disease are awaited.

Etiology remains the major problem for research in BEN. In BEN the results of molecular biological investigations will allow the discovery of genetic markers of BEN, permitting early detection of BEN-predisposing mutations and identification of susceptible individuals who may be at risk of exposure to the environmental agents.

CHN has now been reported in several countries all over the world. Aristolochic acid causes a rapid, progressive tubulointerstitial nephritis and urothelial cancer. There is a trend to speak about the aristolochic acid nephropathy instead of CHN. Aristolochic acid is included in a number of Chinese herbs, and all herbal preparations designated for human use should be subjected to stringent pharmacological and toxicological testing as conventional treatments.

On the basis of clinical, morphological and up-to-date etiologic studies AN, CHN and BEN are separate chronic tubulointerstitial kidney diseases, frequently associated with urothelial malignancy.

Key words: *Analgesic nephropathy, Balkan endemic nephropathy, Chinese herbs nephropathy, tubulointerstitial kidney disease, urothelial cancer, analgesic drugs, aristolochic acid, nephrotoxicity*

Introduction

At present analgesic nephropathy (AN), Balkan endemic nephropathy (BEN) and Chinese herbs nephropathy (CHN) are the only three chronic tubulointerstitial kidney diseases frequently associated with urothelial malignancy. The similarity of morphology and clinical features of CHN and BEN has raised the possibility of a common aetiology, and CHN was suggested as a clue for the etiology of BEN.

Analgesic nephropathy

AN, first described in Switzerland in 1953, is particularly prevalent in some European countries and Australia. AN is a form of chronic renal disease characterized by renal papillary necrosis and chronic interstitial nephritis, uroepithelial tumors, and atheromatous renal artery stenosis. The disease results from prolonged abuse of analgesic mixtures containing aspirin or phenazone in combination with phenacetin, paracetamol, caffeine, or codeine phosphate (1-3). However, AN may also result from the therapeutic misuse of nonsteroidal anti-inflammatory drugs (4).

AN appears to be a disease of the 20th century. AN is a significant cause of end-stage kidney failure, and its contribution to terminal failure care program varies from 3% in Europe to approximately 20% in Australia. AN occurs six to seven times more frequently in women than in men. Its peak incidence is between the ages of

40 and 60, and an alternative diagnosis should be considered if a patient is under the age of 30. AN is a part of a wider clinical syndrome, including AN, gastric ulcer, anemia, psychiatric disturbances, cardiovascular and gonadal disturbances, and premature aging (5).

There is a documented causal relation between analgesic consumption and renal disease, and the changes of AN can be reproduced in animal models. Animal experiments show that most analgesics, individual or in combination, can cause AN, and that their toxicity is cumulative.

Aspirin and salicylates are concentrated especially in the medulla during antidiuresis. Aspirin acetylate components of the cell cytoplasm deplete intracellular glutathione, inhibit prostaglandin synthetase, and reduce medullary lipogenesis by irreversibly blocking fatty acid cyclooxygenase. Paracetamol, the major metabolite of phenacetin, also concentrates in the renal medulla during antidiuresis. It is metabolised to a highly reactive intermediate, which covalently binds to tissue proteins, especially when glutathione concentrations are reduced. Paracetamol also causes marked depletion of serum sulfate limiting its availability for medullary synthesis of proteoglycans and glycosaminoglycans. These biochemical effects result in cytotoxic cell death, medullary ischemia and renal papillary necrosis, and are consistent with a synergistic nephrotoxicity of aspirin and paracetamol. Phenacetin, however, does not concentrate in the medulla, and its nephrotoxicity is related to its metabolite, paracetamol. Environmental and genetic factors may influence predisposition of analgesic abusers to renal damage. The importance of these factors is emphasized by the absence of renal damage in some heavy analgesics abusers who tend to be young and obese.

Chinese herbs nephropathy

CHN was described in 1993 by Vanherweghem et al. (6) in Belgian women who followed the same slimming regimen that included the Chinese herbs *Stephania tetrandra* and *Magnolia officinalis*. In the first report on CHN, a phytochemical analysis of slimming pills has disclosed *Magnolia officinalis* alkaloids, but alkaloids derived from *Stephania tetrandra* could not be identified, suggesting that this herb might have been replaced by other, but toxic plant material (6). In the January 1994 issue of Lancet Vanhaelen et al. (7) have established that most of the herb powders delivered to Belgium, from July 1990 to August 1992, under the name of *Stephania tetrandra* contained aristolochic acid (AA) and not the expected tetrandrine. The data were in accord with analysis done in Hong Kong on Chinese herbs delivered to Belgium (8). This analysis revealed that terminal renal failure observed in Belgium has probably resulted from the administration of *Aristolochia fangchi* powder instead of *Stephania tetrandra*. The tragic replacement of herb powders in Belgium has produced over 80 cases of CHN (9). The characteristics of the disease have been published: clinical presentation, natural course, biochemical characteristics, kidney morphology, urothelial cancer, extrarenal complications, treatment including cotricosteroids, dialysis and kidney transplantation (10). On the basis of morphological and clinical grounds CHN was found similar to BEN (11) . A common etiologic agent, aristolochic acid, was suspected.

Balkan endemic nephropathy

BEN is a chronic tubulointerstitial kidney disease occurring at a high rate in some areas of Serbia, Bosnia, Croatia, Bulgaria and Romania, along the affluents of the Danube River (12).

Ochratoxin A is a mycotoxin demonstrated to be responsible for porcine nephropathy in northern Europe (13). Porcine nephropathy is primarily a tubulointerstitial disease, similar to BEN in many ways, suggesting a common causal relationship. The most pronounced food-born exposure to ochratoxin has been found in the area an Croatia where BEN is prevalent (14). The associated nephrotoxicity and carcinogenicity (15) of ochratoxin A recently described make this hypothesis particularly attractive. It induces DNA single-strand breaks and has been shown to be carcinogenic in two rodent species. Oral administration of ochratoxin A to mice has been followed by formation of several DNA adducts especially in the kidney indicating that kidney is the main target of the genotoxicity of ochratoxin A (15). Several ochratoxin-DNA adducts were detected in kidney and bladder cancer tissues of patients from Bulgaria (16). However, ochratoxin A induces renal parenchymal carcinoma in mice, but it is not a potent carcinogen, nor is there experimental evidence to link it to upper urothelial cancer (17). The lowest doses of ochratoxin A that are toxic in experimental animals are four to five times higher than those found even in hyperendemic regions (18). This finding casts doubt on the hypothesis that ochratoxin A is the sole cause of BEN. Indeed, to date there is no evidence that ochratoxin is responsible for any kidney disease or urothelial cancer in humans.

Feder et al. studied the geochemistry of the areas where Balkan nephropathy is endemic (19). They found that endemic settlements are located near weathered coal deposits. Most endemic foci have Pliocene age lignites in their vicinity. Pliocene age coals are 1.6 to 5.3 million years old and are the youngest coals in the Balkans. These low-rank coals in the Balkans still retain many of the complex organic compounds contained in the decaying plant precursors of the coal. Weathering of the low-rank coals could generate complex mixtures of water-soluble hydrocarbons, which are present in the drinking water of the shallow farm wells. Preliminary results from qualitative chemical analyses of drinking water from shallow farm wells in endemic settlements indicate the presence of soluble polar polycyclic aromatic hydrocarbons and aromatic amines, from example

naphthylamine, aniline, antracene, pyrene. Many of these compounds are known to be carcinogenic and could also cause urothelial cancer.

A viral aetiology has been suggested by the common occurrence of BEN and urothelial cancer in the same population (12). A slow coronavirus infection in man with BEN has been recently demonstrated, however, the causal relationship was not established (20).

Epidemiological and genetic studies have supported the genetic predisposition to BEN. The candidate genes have been localized to a region between 3q25-3q26, 3q BEN-marker being detected in BEN patients and in some healthy relatives with initial morphological changes peculiar to BEN (21,22). The impact of environmental triggers on individuals genetically predisposed to BEN was demonstrated by the higher frequency of folate sensitive Fra sites, spontaneous and radiation-induced chromosome breakages in BEN patients than in controls (23). Three bands with increased frequencies of spontaneous and induced aberrations contain oncogenes. The frequent association of BEN and urothelial cancer can be explained by the chromosomal hypothesis of oncogenesis.

Aristolochic acid

Some 30 years ago aristolochic acid was suggested as the etiologic agent of BEN. Ivic has found aristolochic acid in flour obtained from wheat contaminated with seeds of *Aristolochia clematitis* in endemic regions (24). He conducted a survey of the geographical distribution of the plant, *Aristolochia clematitis*, in the endemic area. Focal tubulointerstitial changes were observed in rabbits poisoned by giving them orally various amounts of flour made from ground dried *Aristolochia* seeds. These changes corresponded to the changes characteristic of BEN.

The active principle of herbal drugs derived from *Aristolochia* species is aristolochic acid (AA). Plant extract AA is a mixture of structurally related nitrophenanthrene carboxylic acids, with AAI being the major component. AA was shown to be nephrotoxic in humans and rabbits (24,25), being a strong carcinogen in rodents (26). Mutagenic and carcinogenic responses were found associated with the formation of AA DNA adducts (27).

Aristolochic acid was previously described as a causal agent of Balkan endemic nephropathy (24). AA was found in the flour obtained from wheat contaminated with seeds of *Aristolochia clematitis* in the endemic region. The hypothesis that AA is the causal factor of BEN has not been substantiated by the determination of toxin and AA-derived DNA adducts in the blood, urine and kidney tissue of patients.

The etiology of CHN is still puzzling. The amount of ingested AA, calculated on the basis of batch analysis (7), is in the range prescribed in traditional Chinese medicine, without untoward effects (28). Nephrotoxic doses of AA given experimentally to rats are several times higher that ingested by slimming pills (29). A recent study demonstrated the DNA adduct of AAI in renal tissue of 5 patients with CHN, thus establishing that CHN is indeed associated with the presence of AA (30). However, the fact that the amount of ingested AA calculated from the batch analysis is minimal raises the possibility that AA possibly has a toxic effect synergistic with some other compound(s) included in the slimming regimen (9). The slimming tablets also included two appetite suppressants, fenfluramine and diethylpropion, a serotonin antagonist and a sympaticomimetic drug, respectively (6). Both of these drugs have vasoconstrictive properties, and in CHN tubulointerstitial renal disease may have been caused by the ingestion of aristolochic acid, a potent nephrotoxic and genotoxic agent, on a background of fenfluramine/diethylpropion-related sustained renal vasoconstriction.

Similar morphological and clinical findings in AN, CHN and BEN

Several similar clinical and morphological findings in CHN and BEN are demonstrated (Table 1). Similar renal morphologic changes by light/electron microscopy, and immunohistology in CHN and BEN were described (11,31-33). The most severe lesions were encountered in the superficial cortex. Tubular atrophy, interstitial fibrosis, and renal vascular changes predominated. The glomeruli were relatively spared in comparison with tubules. Immunofluorescent staining disclosed no significant abnormalities.

Table 1. Similar features of AN, BEN and CHN

Normal arterial blood pressure
Early and severe anemia
Tubular functional abnormalities
LMW proteinuria
Glucosuria
Renal tubular atrophy, interstitial fibrosis and vascular changes
Cellular atypia of the urothelium and urothelial malignancy
Lack of recurrence after kidney transplantation

Arterial blood pressure was initially normal in most of the patients (10,12).

Anaemia was more severe than expected for the degree of renal failure, probably as a result of early destruction of peritubular cells producing erythropoietin (10,12).

Proximal tubular injury results in low molecular weight proteinuria and glycosuria (10,12,34).

An increased incidence of urothelial cancer was observed in patients with BEN, in their healthy family members, and in inhabitants of endemic settlements (35). CHN was associated with urothelial atypia and transitional cell carcinoma of the urothelium (36). It was suggested that the deoxyadenosine-AAI DNA adducts are responsible for the urothelial cancer in CHN (29). A high incidence of transitional cell carcinoma of renal pelvis, ureter and urinary bladder has been observed in

Table 2. Different features of AN, BN and CHN

	Analgesic nephropathy	Balkan nephropathy	Chinese herbs nephropathy
Familial character	No	Important feature	No
Rate of progression	Slow	Very slow	Rapidly progressive
	> 10–15 years	> 15–20 years	6 months – 2 years
Extrarenal manifestations			
Aortic insufficiency	Not described	Not described	Documented in 40%
Peritoneal fibrosis	Not described	Not described	Described
Periureteral fibrossis	Not described	Not described	Described
Kidney imaging	Shrunken kidneys	Shrunken kidneys	Shrunken kidneys
	Irregular contours	Smooth surface	Irregular contours
	Calcifications-papillary	No calcifications	No calcifications
Urinary deposit	Aseptic leukocyturia	Scarce deposit	Aseptic leukocyturia
Etiology	Analgesics	Unkonown	Aristolochic acid + vasoconstrictive substances
Corticosteroid treatment	Not described	Not described	Slowed impairment of GFR

patients with AN (1,37,38). Development of the cancer has been related to the carcinogenic effect of 2-hydroxy and N-hydroxy metabolites of phenacetin. Urothelial cancer occurs with an average latency period of 21-30 years, frequently arriving simultanously at different sites of the urinary tract.

BEN as well as AN and CHN did not recur after kidney transplantation (10,39). However, the observation period is short and the number of grafted CHN patients is small for a definite conclusion.

Different features of AN, BEN and CHN

Familial character of BEN has been observed since its description in 1957 (7); however, subacute toxic effect of AA was described in a population of a single Belgian slimming clinic (Table 2).

Progression to end-stage renal disease (ESRD) is faster in CHN than in other interstitial kidney diseases (10), including AN and BEN (12). The 2-year actuarial survival rate without ESRD was 17% in CHN versus 74% in other interstitial kidney diseases (10). However, an even indolent course of CHN was rarely observed (40). Chinese herbs may also induce a protracted chronic renal failure. Progression to ESRD in BEN is slow, over 10 or more years from the incipient renal failure (12).

In CHN the fibrotic process was not confined to the kidneys only but was extended to pelvis and ureter-periureteral fibrosis (41), peritoneal membrane-submesothelial fibrosis (42), and aortic valve, presenting as aortic insufficiency (10). Valvular heart disease has been recently incriminated to fenfluramine and diethylpropion, appetite suppressants, included in slimming tablets (43,44). The extrarenal manifestations were not observed in BEN.

Aseptic leukocyturia was found in 40% of cases with CHN (10) and AN (3).

Kidney atrophy in BEN is symmetric with a smooth outline (7); in CHN the kidneys are asymmetric in 54% of cases, with irregular outlines in 31% of cases (5); kidney atrophy is asymmetric in AN, with irregular outline (3,5).

Kidney morphology, though similar, has some different features (Table 3). In CHN extensive interstitial fibrosis develops with marked tubular atrophy and disappearance of atrophic tubular structures (11).

Table 3. Kidney morphology in AN, BN and CHN

	Analgesic nephropathy	Balkan nephropathy	Chinese herbs nephropathy
Gross morphology			
Kidney atrophy	Asymmetric	Symmetric	Asymmetric
Outline	Irregular	Smooth	Irregular
Kidney morphology*			
Tubular atrophy	2	3	3
Interstitial fibrosis	2	2	3
Cellular infiltration	2	1	1

* Graded from 1 (present) to 3 (extensive)

It was reported that steroid treatment could slow impairment of renal function in CHN (45). This has not been described in BEN.

Conclusions and future research

Etiology remains the major problem for research in both BEN and urothelial cancer. In BEN, only a few described environmental factors should be considered. A preliminary case study has shown that avoidance of aetiological factors is associated with slowed progression of kidney disease (46). AA DNA adducts should be searched in urine, and kidney tissue or urothelial malignancy of the diseased from endemic settlements. Negative results will rule out the role of AA in BEN; however, the positive one could favour the hypothesis that AA could be one of the etiologic factors or cofactors in BEN and urothelial cancer. The results of molecular biological investigations will allow the discovery of genetic markers of BEN and associated urothelial cancer, permitting early detection of BEN-predisposing mutations and identification of susceptible individuals who may be at risk of exposure to the environmental agents.

In CHN, proper identification of all plant toxins in the pills used for slimming regimen seems necessary. Experimental studies with AA and other phytotoxins alone and in combination, possibly with drugs used for

slimming regiment, could reveal the cause of this tragic event leading over 80 women to end-stage renal disease. Genetic predisposition to these plant toxins should be revealed, since not all persons taking slimming pills developed CHN. CHN has now been reported in several countries all over the world. Aristolochic acids cause a rapid, progressive tubulointerstitial nephritis and urothelial cancer. There is a trend to speak about the aristolochic acid nephropathy instead of CHN. Aristolochic acid is included in a number of Chinese herbs, and all herbal preparations designated for human use should be subjected to stringent pharmacological and toxicological testing as conventional treatments.

AN is characterized by renal papillary necrosis and chronic interstitial nephritis, urothelial cancer, and atheromatous renal artery stenosis. Its contribution to end stage renal replacement programs varies from 3% in Europe to 20% in Australia. There is a documented causal relation between analgesic abuse and renal disease, and the changes of AN can be reproduced in animal models. Animal experiments show that most analgesics, individual or in combination, can cause AN, and that their toxicity is additive. AN due to analgesic mixtures and possibly due to nonsteroidal anti-inflammatory drugs taken over long periods of time represent a preventable cause of chronic renal failure. Classical AN appears to be markedly less common than 20 years ago. Reduction in exposure to phenacetin and combination preparations, however, has not eliminated AN. The exact prevalence of this disease in various countries all over the world is still unclear fifty years after the original description of this entity. The magnitude of analgesic exposure-related renal disease today is unclear both as a primary cause of disease and as a cofactor of renal disease of known etiology. National studies to evaluate the prevalence of AN among incident ESRD patients, leading to national programs to combat this preventable kidney disease are strongly encouraged.

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