Preventing Aristolochic Acid Nephropathy

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Reports of an epidemic of rapidly progressive fibrosing interstitial nephritis first surfaced in the early 1990s in a cohort of Belgium women (1). The causative agent was found to be aristolochic acid (2), a family of compounds found in the plant genus *Aristolochiacaea*, including the *Aristolochia* and *Asarum* species (also known as birthwort or Dutchman's pipe). Aristolochic acid has been an ingredient in Chinese herbal remedies commonly used to treat an assortment of illnesses, including eczema, pneumonia, stroke, and hepatitis. It was classified a human (class I) carcinogen by the World Health Organization International Agency for Research on Cancer in 2002 and is associated with a characteristic pattern of nephrotoxicity termed aristolochic acid nephropathy (AAN) and urothelial malignancy (3,4).

The role of environmental exposure to aristolochic acid in the etiology of Balkan endemic nephropathy (BEN) is now well documented. The striking pathologic similarities between the first described patients with AAN and BEN were noted in the original report of the Belgian outbreak (1). Indeed, environmental exposure to aristolochic acid had first been suggested as a cause of BEN in 1969, when Ivić (5) found contamination of wheat flour by the seeds of *Aristolochia clematitis*, a weed that is common in wheat fields in endemic areas (6). The molecular link between AAN and BEN was first shown by Arlt *et al.* (7), establishing that aristolochic acid–specific DNA adduct formation occurred in a patient from an endemic region. Additional work extended these findings and showed characteristic *p53* mutations and urothelial tumor development, with BEN being pathologically indistinguishable from AAN caused by Chinese herbal products (8,9). Indeed, BEN is now more appropriately considered as a specific geographically defined form of AAN (10,11).

Although the exact extent of AAN is unknown, case series have been reported in the United States, Europe, Australia, and Asia, suggesting that this is a global health problem (11,12).

At present, there are no strict diagnostic criteria to aid the clinician. The majority of patients present with renal insufficiency, anemia, a urine sediment with few erythrocytes and leukocytes, and mild proteinuria (typically <1.5 g/2 d). Renal tract ultrasonography reveals shrunken kidneys, which can be asymmetric and irregular in cortical outline. Histologic findings include extensive interstitial fibrosis associated with tubular atrophy, low numbers of chronic inflammatory cells decreasing from the outer to the inner cortical labyrinth, and fibrous hyperplasia of arteriolar walls. Multifocal urothelial atypia is observed in almost all patients, and 40%–46% of patients have multifocal, often bilateral transitional cell carcinoma *in situ*, usually located in the upper urinary tract (13). Ingestion of aristolochic acid can be confirmed by phytochemical analysis, and DNA adduct analysis can be used to identify the presence of aristolochic acid DNA adducts in renal or urinary tract tissue.

There is no definitive treatment for this disease; however, there is some evidence that steroid treatment may modify progression of CKD (14,15). General supportive management is similar to that of other causes of CKD. In light of the increased risk of urothelial malignancy, patients should be offered yearly surveillance with computerized tomography imaging and ureteroscopy, with bilateral nephroureterectomy considered at the point of requiring RRT followed by surveillance for bladder carcinoma with annual rigid cystoscopy.

With the majority of patients progressing rapidly to ESRD and the absence of definitive treatment, the primary objective has been prevention of AAN. In fact, the US Food and Drug Administration Agency banned all herbal remedies containing aristolochic acid in 2000. Despite these measures, Vaclavik *et al.* (16) recently found that the two different forms of aristolochic acid were detected in over 25% of samples tested in a survey of 30 herbal products available to order through the internet (17). The decline in renal function in BEN occurs over 15–20 years, possibly related to the cumulative effect of prolonged low-grade exposure to aristolochic acid (6,10,18). In this issue of *CJASN*, Jelaković *et al.* (19) test the hypothesis that Bosnian immigrants who settled in an endemic area of Croatia 15–30 years ago are at lower risk of developing AAN because of reduced exposure to aristolochic acid. This cross-sectional observational study with a 5-year study period focused on the incidence of CKD (defined as eGFR<60 ml/min per 1.73 m^2) and proximal tubule damage (PTD; defined as α1-microglobulin to creatinine $\geq$31.3 mg/g). Exposure to aristolochic acid and farming practices were assessed using a survey. The results of this study suggest a significantly lower prevalence of CKD and PTD in the Bosnian immigrant population. Jelaković *et al.* (19) conclude that Bosnian immigrants residing in endemic areas are significantly less exposed to dietary ingestion of aristolochic acid than in the past and confirm the relationship between reduced exposure to aristolochic acid in endemic areas and reduced prevalence of PTD.

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The strengths of this study are its sample size of over 2000 and participant uptake rates. In any observational study, recall bias must be considered, particularly in the context of recall over a 3-decade period. By using a door-to-door approach, Jelaković *et al.* (19) have attempted to reduce selection bias; however, this may not have been completely eliminated.

Aristolochic acid exposure was considered positive if the *Aristolochia* plant was observed in farming fields or *Aristolochia* seeds were seen among wheat seeds. The current literature supports that the ingestion of aristolochic acid is the primary etiologic agent in AAN and not environmental exposure (8,11,18). Confirmation of exposure using phytochemical analysis may be a more robust method of defining exposure, although the practicality of this approach in a large sample size may prove a limiting factor.

In this study, Bosnian immigrants had lived in endemic areas for 15–21 years, and Jelaković *et al.* (19) considered >15 years an adequate time period to ingest a cumulative toxic dose of aristolochic acid. Although there have been advances in understanding the epidemiology and molecular pathogenesis of AAN, there is no exact quantification of the toxic dose of aristolochic acid or the duration of exposure necessary for the development of AAN or urothelial malignancy. However, higher cumulative exposures are clearly associated with greater risks of developing AAN (11,20).

It has been proposed that genetic susceptibility plays an etiologic role in the development of AAN, raising the possibility that the genetic background of the Bosnian immigrant population confers a degree of protection against the effect of aristolochic acid exposure (18).

The importance of awareness and recognition of AAN cannot be overemphasized. Legislative changes allowing regulation of herbal supplements and other food substances for the presence of aristolochic acid along with advances in farming techniques will help to decrease the incidence of AAN. The worldwide distribution of reported patients with AAN and the likely underreporting and underdiagnosis of AAN in countries where *Aristolochia* species are known to be used support the need for united global public health initiatives to eradicate this entirely preventable disease.

Disclosures

None.

References

1. Vanherweghem JL, Tiedemann C, Abramowitz D, Depierreux M, Vanhaelen-Fastre R, Vanhaelen M, Dratwa M, Richard C, Vandervelde D, Verbeelen D, Jadoul M: Rapidly progressive interstitial renal fibrosis in young women: Association with slimming regimen including Chinese herbs. *Lancet* 341: 387–391, 1993
2. Lord GM, Tagore R, Cook T, Gower P, Pusey CD: Nephropathy caused by Chinese herbs in the UK. *Lancet* 354: 481–482, 1999
3. World Health Organisation International Agency for Research on Cancer: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*, Lyon, France, IARC Press, 2002, p 82
4. Lord GM, Cook T, Arlt VM, Schmeiser HH, Williams G, Pusey CD: Urothelial malignant disease and Chinese herbal nephropathy. *Lancet* 358: 1515–1516, 2001
5. Ivić M: Etiology of endemic nephropathy. *Lijec Vjesn* 91: 1273–1281, 1969
6. Hranjec T, Kovac A, Kos J, Mao W, Chen JJ, Grollman AP, Jelaković B: Endemic nephropathy: The case for chronic poisoning by aristolochia. *Croat Med J* 46: 116–125, 2005
7. Arlt VM, Ferluga D, Stiborova M, Pfohl-Leszkowicz A, Vukelic M, Ceovic S, Schmeiser HH, Cosyns JP: Is aristolochic acid a risk factor for Balkan endemic nephropathy-associated urothelial cancer? *Int J Cancer* 101: 500–502, 2002
8. Arlt VM, Stiborová M, vom Brocke J, Simões ML, Lord GM, Nortier JL, Hollstein M, Phillips DH, Schmeiser HH: Aristolochic acid mutagenesis: Molecular clues to the aetiology of Balkan endemic nephropathy-associated urothelial cancer. *Carcinogenesis* 28: 2253–2261, 2007
9. Grollman AP, Shibutani S, Moriya M, Miller F, Wu L, Moll U, Suzuki N, Fernandes A, Rosenquist T, Medverec Z, Jakovina K, Brdar B, Slade N, Turesky RJ, Goodenough AK, Rieger R, Vukelić M, Jelaković B: Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A* 104: 12129–12134, 2007
10. Gökmen MR, Lord GM: Aristolochic acid nephropathy. *BMJ* 344: e4000, 2012
11. Gökmen MR, Cosyns JP, Arlt VM, Stiborová M, Phillips DH, Schmeiser HH, Simmonds MS, Cook HT, Vanherweghem JL, Nortier JL, Lord GM: The epidemiology, diagnosis, and management of aristolochic acid nephropathy: A narrative review. *Ann Intern Med* 158: 469–477, 2013
12. Debelle FD, Vanherweghem JL, Nortier JL: Aristolochic acid nephropathy: A worldwide problem. *Kidney Int* 74: 158–169, 2008
13. Nortier JL, Schmeiser HH, Muniz Martinez MC, Arlt VM, Vervaet C, Garbar CH, Daelemans P, Vanherweghem JL: Invasive urothelial carcinoma after exposure to Chinese herbal medicine containing aristolochic acid may occur without severe renal failure. *Nephrol Dial Transplant* 18: 426–428, 2003
14. Martinez MC, Nortier J, Vereerstraeten P, Vanherweghem JL: Steroid therapy in chronic interstitial renal fibrosis: the case of Chinese-herb nephropathy. *Nephrol Dial Transplant* 17: 2033–2034, 2002
15. Vanherweghem JL, Abramowicz D, Tielemans C, Depierreux M: Effects of steroids on the progression of renal failure in chronic interstitial renal fibrosis: a pilot study in Chinese herbs nephropathy. *Am J Kidney Dis* 27: 209–215, 1996
16. Vaclavik L, Krynitsky AJ, Rader JI: Quantification of aristolochic acids I and II in herbal dietary supplements by ultra-high-performance liquid chromatography-multistage fragmentation mass spectrometry. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 31: 784–791, 2014
17. US Food and Drug Administration: *Dietary Supplements: Arsitolochic Acid,* US Food and Drug Administration, 2001. Available at: http://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/ucm096388.htm. Accessed December 12, 2014
18. Stefanovic V, Toncheva D, Atanasova S, Polenakovic M: Etiology of Balkan endemic nephropathy and associated urothelial cancer. *Am J Nephrol* 26: 1–11, 2006
19. Jelaković B, Vuković Lela I, Karanović S, Dika Z, Kos J, Dickman K, Sekoranja M, Poljičanin T, Mišić M, Premužić V, Abramović M, Matijević V, Miletić Medved M, Cvitković A, Edwards K, Fuček M, Leko N, Teskera T, Laganovic M, Čvorišćec D, Grollman AP: Chronic dietary exposure to aristolochic acid and kidney function in native farmers from a Croatian endemic area and Bosnian immigrants. *Clin J Am Soc Nephrol* 10: 215–223, 2015
20. Nortier JL, Martinez MC, Schmeiser HH, Arlt VM, Bieler CA, Petein M, Depierreux MF, De Pauw L, Abramowicz D, Vereerstraeten P, Vanherweghem JL: Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). *N Engl J Med* 342: 1686–1692, 2000

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