Mysterious Balkan Disease’s Likeliest Risk Factor Also in Chinese Medicines

Scientists speculate that the highest risk factor for a kidney disease common to five Balkan nations is a plant commonly used in various Chinese herbal medicines.

Washington D.C. – Risk analysts have examined extensive health evidence to conclude that a toxin produced by a weed commonly found in certain grain fields in Balkan countries, and also used in Chinese herbal medicines, is the most likely cause of a fatal kidney wasting disease often found there. The results may also shed light on related diseases worldwide.

In their new paper, “Evaluating Weight of Evidence in the Mystery of Balkan Endemic Nephropathy” (BEN), Felicia Wu of the Michigan State University Department of Food Science and Human Nutrition and Travis Bui-Klimke formerly of the University of Pittsburgh Graduate School of Public Health comprehensively analyzed the human data on the disease. BEN is endemic in certain rural regions of Bosnia, Croatia, Serbia, Bulgaria, and Romania. Their analysis, supported by the U.S. National Cancer Institute and National Institutes of Health, used the widely accepted nine Bradford Hill Criteria (BHC) for investigating and defining causality in epidemiology studies. Using the BHC, they concluded that aristolochic acid (AA) from Aristolochia weeds has the strongest weight of evidence as BEN’s cause among various risk factors investigated. The paper recently appeared in the online version of Risk Analysis, published by the Society for Risk Analysis.

More broadly, the researchers note that two studies also have raised concerns about global AA exposure through Aristolochia plant use in a variety of herbal medicines. In the 1990s, for example, approximately 1800 Belgian women who consumed herbal medicines as part of a weight loss program “developed rapidly progressive renal interstitial fibrosis leading to chronic renal failure.” Originally focused on BEN as a mysterious but geographically contained disease, the authors conclude, their study “has expanded to reveal the much larger potential role of this environmental toxin in causing human disease worldwide.”

Academic and clinical researchers have debated BEN’s etiology for decades, but the disease has unusual facets and thus its potential risk factors have been puzzling. Besides AA, researchers have explored a variety of possible agents, including exposure to metals and metalloids, viruses and bacteria, and ochratoxin A (OTA), a fungal toxin common in many foods, such as cereal
grains. Bui-Klimke and Wu analyzed the weight of evidence for each of these and concluded that OTA may play a contributory role but is unlikely on its own to cause BEN.

First described in Bulgaria in the scientific literature in the 1950s, BEN caused individuals, usually aged in their 50s, to develop symptoms of uremia, a buildup of nitrogenous waste products in the blood that signal renal failure. The irreversible renal disease would lead to death. Certain villages have a high BEN prevalence, but other villages only a few kilometers apart may be unaffected. Affected families have a pattern of disease without genetic inheritance. BEN has a long incubation period, initially manifesting after a 15-20-year residence in an endemic area; it has equal male-female distribution and incidence across ethnic groups, and it is associated with upper urothelial tract carcinoma. Although evidence has suggested that BEN’s prevalence may be decreasing over time, observations also indicated that BEN’s prevalence in the Kolubara River region in Serbia increased from 6.4 percent in 1971 to 8.9 percent in 2002. For Croatia, current estimates suggests BEN’s prevalence ranges from 0.3 to 2.3 percent, with a mean of 1 percent.

“The toxicological and epidemiological evidence linking AA with BEN are convincing in terms of the strength of association, consistency, specificity, temporality, dose-response relationship, coherence, experiment, and analogy,” the authors state, citing the nine BHC. The scientific literature provided “consistent and convincing evidence of the dose-dependent relationship between AA exposure and BEN,” as well as BEN-related diseases, “in multiple populations worldwide,” the authors note. No studies contradicted their findings. Overall, AA received “high” scores for eight of the nine BHC.

In their concluding discussion, the authors state that because various herbal medicines use Aristolochia plants, the plants’ “associated human nephropathies may cause a greater burden of disease worldwide than previously understood.”

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