BALKAN ENDEMIC NEPHROPATHY: THE COMPLEX EQUATION OF MULTIFACTORIAL ETIOLOGY

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A fatal kidney disease, Balkan endemic nephropathy (BEN) has been plaguing certain geographically restricted rural areas of the Balkan Peninsula for decades. More than 50 years have passed since the initial medical description of the disease and although its etiology is still unclear several advances have been recently made in unraveling some potential causative factors. A phytotoxin, called aristolochic acid (AA) and produced by the plant Aristolochia clematitis (birthwort) has been proposed to be responsible for the kidney failure and the associated urothelial cancers and more recent data has pointed to the presence of biomarkers (DNA-AA adducts) of previous exposure to aristolochic acid of BEN patients. However, such adducts can be the mere consequence of the presence of Aristolochia clematitis in high abundance in the endemic, but as well in nonendemic, areas. However, the exposure pathway to AA is unclear. Wheat flour contamination with the toxin has been proposed but if this is true or not it is still an open question, as long as similar contamination and similar exposure pathways may potentially occur in many other places around the world, where BEN is not present. Aristolochia clematitis could be an important risk factor for BEN in a genetically susceptible population, but an additional, geographically confined, agent has to contribute in a synergistic or additive way to the etiology of the disease. Our original proposal was that Pliocene lignite deposits, present in and around the endemic areas would provide the geographic character of the disease. The Pliocene lignites are immature coals, capable of leaching large amounts of potentially nephrotoxic and carcinogenic organics that are transported into the water sources used by the villagers. Such low and high molecular weight compounds, may set up the stage for other toxins, like AA, to reach a threshold effect in causing BEN, in a multifactorial disease induction pattern. Extracts of Pliocene lignites from endemic area and high molecular weight organic concentrates of endemic water samples are able to inhibit kidney cell growth and induce cell death at higher concentrations. Other effects include expression downregulation and intracellular reorganization of actin and stimulation of multidrug resistance protein 1 expression. All these effects may sensitize kidney cells and make them more susceptible to additional environmental insults, resulting in the BEN phenotype.

Keywords: Balkan, endemic, nephropathy.