Toward a Comprehensive Hypothesis of Chronic Interstitial Nephritis in Agricultural Communities

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Over the past 20 years, there has been an increase in chronic interstitial nephritis in agricultural communities (CINAC) not associated with traditional risk factors. This disease has become an important public health problem and is observed in several countries in Central America and Asia. CINAC predominantly affects young male farmers between the third and fifth decades of life with women, children, and adolescents less often affected. Clinically, CINAC behaves like a chronic tubulointerstitial nephropathy but with systemic manifestations not attributable to kidney disease. Kidney biopsy reveals chronic tubulointerstitial nephritis with variable glomerulosclerosis and mild chronic vascular damage, with the severity depending on sex, occupation, and CKD stage. The presence of toxicological, occupational, and environmental risk factors within these communities suggests a multifactorial etiology for CINAC. This may include exposure to agrochemicals, a contaminated environment, repeated episodes of dehydration with heat stress, and an underlying genetic predisposition. An understanding of these interacting factors using a multidisciplinary approach with international cooperation and the formulation of a comprehensive hypothesis are essential for the development of public health programs to prevent this devastating epidemic.

Key Words: Chronic interstitial nephritis in agricultural communities, Chronic kidney disease of unknown causes (CKDu), Pesticides, Dehydration, Heat stress

Diabetes mellitus and hypertension are the two leading causes of CKD across the globe, particularly in the developed world. In developing countries, these well-known etiologies of CKD can be accompanied or supplanted by other causes of glomerular and tubulointerstitial diseases such as infections or injury due to nephrotoxic drugs, herbal supplements, environmental toxins, and occupational exposure to pesticides. These factors all can contribute to the high burden of CKD in developing nations.[1] During the past two decades in certain locations in Latin America and Asia, there has been an increase in the prevalence of CKD affecting agricultural communities, specifically targeting young male agricultural workers who do not have the traditional risk factors of diabetes and hypertension. This recently recognized form of CKD has been termed chronic interstitial nephritis in agricultural communities (CINAC) and has become an important and devastating public health issue, particularly in Central America.[2-8] In fact, according to The Pan American Health Organization, Nicaragua and El Salvador have CKD-related estimated mortality rates of 42.8 and 41.6 deaths per 100,000, respectively, which is fourfold higher than any other country in the world with respect to mortality due to kidney disease. In El Salvador, CKD is the second most common cause of death in men, with males affected at three times the rate of females.[9]

EPIDEMIOLOGICAL CHARACTERISTICS AND PATHOGENESIS

In El Salvador, a number of epidemiological studies have estimated the prevalence of CINAC in farming communities to be between 15% and 21% with a 9% to 13% prevalence of chronic renal failure. Less than half of those affected have diabetes mellitus or hypertension. While the disease predominates in men, it also affects women, children, and adolescents who live in these farming communities regardless of whether they work in agriculture, and evidence suggests that the kidney disease may begin in the early stages of life. This increased prevalence of CKD has been observed in farming communities both in the highlands and lowlands of El Salvador, suggesting there may be multiple factors involved.[3,10,11] Interestingly, similar findings of CINAC have been reported worldwide, particularly in Sri Lanka, India, and Egypt. The etiology of this epidemic of CKD remains unclear but is thought to include exposure to toxins such as pesticides and herbicides and repeated episodes of dehydration which occur in all affected populations. Other similar risk factors that have been identified in those affected in differing locations include agricultural work, male sex, age, poverty, use of well water, over use of NSAIDs, and histories of snake bites and infections to a more limited degree.[12,13]

In farming communities, heavy metals (cadmium and arsenic) and pesticides are present in well water, floors in homes, and farmlands and are more concentrated in

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crop areas. These likely accumulate due to extensive use of pesticides, including those which have been banned in many developed countries, to improve crop yield. The increase in CKD incidence in Central America began approximately 20 years ago, concomitant with a significant increase in the use of toxic agricultural chemicals such as paraquat, glyphosate, triazines, methamidophos, and methyl parathion.[4,5] The nephrotoxic potential of these compounds is known and has been described in the literature.[14-19] Pesticide exposure occurs during farmland application and from pesticide storage in household facilities. During spraying, farmers may inhale or accidentally ingest pesticides and herbicides, and their skin may become contaminated with these toxins due to the lack of outer garment protection. There is an association between self-reported use of carbamate pesticides in a hot and humid environment with a change in kidney-related biomarkers and a reduction in GFR.[20] In the United States, a cohort of 55,580 male licensed pesticide applicators showed a significant association of chronic exposure to specific pesticides with increased risk of developing end-stage kidney disease.[21] Further evidence for a role of toxin exposure is the presence of extrarenal symptoms associated with CINAC including urinary dribbling, abnormalities in arteries by ultrasound, myoclonus and sensorineural deafness.[22] Volcanic soil and other natural contaminants such as arsenic and hard water also may play a role. Although a single metal cannot be linked to CINAC, heavy metals have been found in excessive amounts in the urine of agricultural workers. Jayasumana and associates[5,23] hypothesized that the use of glyphosate, an herbicide and strong metal chelater, in conjunction with arsenic and the consumption of hard water, might be a cause of kidney disease in Sri Lankan agricultural workers.

When agricultural workers' clothes become contaminated with pesticides, family members subsequently may be exposed, particularly women while laundering the family clothing.[24-26] In affected agricultural communities, family members may be exposed via inhalation or ingestion of these toxins due to contamination of household items or the surrounding water and soil. In three farming communities in El Salvador with a significant prevalence of CINAC, children and adolescents have been shown to have an increased incidence of CKD.[10] Ramirez-Rubio and associates[27] showed that adolescents in an affected community in Nicaragua had increased tubular injury associated biomarkers despite no involvement with agricultural work. Other factors may contribute to childhood CKD in these regions such as poor maternal nutrition resulting in low birth weight or a genetic predisposition. In Sri Lanka, a genomewide association study demonstrated an SNP in the gene encoding sodium-dependent dicarboxylate transporter member 3, which conferred increased risk for CINAC with a population attributable fraction of 50% and odds ratio of 2.3.[28]

Repeated episodes of dehydration due to inadequate intake of fluids while engaged in manual labor in a hot humid climate have been proposed as a cause of CINAC, and undoubtedly repeated dehydration may produce kidney damage.[29] Suggested pathogenetic mechanisms for dehydration-induced kidney injury include activation of the aldo reductase-fructokinase pathway in the proximal tubule with subsequent uric acid production resulting in proximal tubular injury; this has been replicated in an experimental model.[30,31] There also may be a role of rhabdomyolysis.[12] Dehydration, caused by inadequate fluid intake in a hot environment, can affect elimination of toxic agents from the blood and increase the concentration of these agents in the kidney medulla, thus contributing to development of kidney injury. While there may be a role for dehydration in this epidemic of CKD, dehydration alone cannot explain the spectrum of this disease, which affects not only male farmworkers, but also men who are not farmworkers, men in the same geographic region who do not work in agriculture, women who are employed and not employed in agriculture, and school age children and adolescents.

CLINICAL SUMMARY

- Chronic interstitial nephritis in agricultural communities (CINAC) typically occurs in young to middle age male farmworkers in regions of Central America and Asia but also may occur in women and children.
- CINAC is a form of tubulointerstitial nephritis and is a major public health crisis in affected countries.
- There are genitourinary, neurologic, and vascular abnormalities in addition to the kidney disease.
- The pathogenesis of CINAC likely is multifactorial including pesticide exposure, heat stress, dehydration, environmental contaminants, effects of low socioeconomic status, and genetic susceptibility.

CLINICAL CHARACTERISTICS

In the early stages of CINAC, patients may be asymptomatic or demonstrate urinary hesitancy, a thin urinary stream and dysuria. Symptoms become more common in CKD 2 and may include genitourinary abnormalities such as nocturia, dysuria, post void dribbling, hesitancy, and foamy urine, as well as systemic symptoms such as arthralgias, abnormal tendon reflexes, muscle cramps, asthenias, decreased libido, and fainting.[22] At this time, there also may be polyuria with elevated urinary magnesium, sodium, calcium, and phosphorous, with resulting serum electrolyte abnormalities including hyponatremia, hypokalemia, hypomagnesemia and hypocalcemia, and metabolic alkalosis. As the disease progresses, these symptoms progressively intensify with worsening of the kidney disease. Urine analysis typically is unremarkable or shows mild proteinuria, likely of tubular origin with increased β2 microglobulin and tubular markers of injury including KIM-1 and NGAL.[22,32,33] Urine culture is negative. Kidney imaging shows changes of CKD and preserved kidney blood flow. No urinary bladder or prostate abnormalities are identified on ultrasound evaluation.[22]