Chronic Kidney Disease of Unknown Etiology Should Be Renamed Chronic Agrochemical Nephropathy

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ABSTRACT

Epidemics of chronic kidney disease not attributable to common causes have recently been observed in Central America and Asia. Since the etiology is unclear, the disease is often known by terms such as *chronic kidney disease of unknown etiology*. There is growing evidence that risk factors include rural agricultural work and agrochemical exposure. The disease should be renamed *chronic agrochemical nephropathy* to highlight the most likely etiology and draw attention to the condition.

KEYWORDS Chronic kidney diseases/etiology; renal insufficiency, chronic/etiology; kidney failure, chronic/etiology; agrochemicals/adverse effects; pesticides/adverse effects; nephropathy; occupational exposure; environmental exposure; environmental health

INTRODUCTION

Several recent reports have drawn attention to the emergence of an epidemic of chronic kidney disease (CKD) not attributed to common causes such as diabetes, hypertension, glomerulonephritis or obstructive nephropathy. The affected populations include regions in Central America, southern Asia, and Egypt. [1–10] Failure to identify a precise biomedical etiology despite years of research has led to a wide range of names: chronic kidney disease of unknown etiology (CKDu), Salvadoran agricultural nephropathy, Mesoamerican epidemic nephropathy, chronic tubulointerstitial disease of Central America, and Udhanam endemic nephropathy.[2,5,8,10]

Although the causes have not been determined definitively, there is mounting evidence implicating compounds used in agriculture. Research suggests that more than 1000 active compounds sold as insecticides, fertilizers, pesticides, herbicides and fungicides (i.e., agrochemicals) provoke harmful effects on human health, including renal damage.[11] Since it is impractical to identify each renal disorder according to the particular offending substance, grouping them under the term agrochemicals is a possible approach; hence the proposed term, *chronic agrochemical nephropathy.*

It is opportune to name this entity as such for three reasons. First, there appear to be identifiable epidemiological, clinical and pathological features common to those affected. Second, a critical mass of evidence has accumulated implicating agrochemicals in the epidemic's causality. And finally, the term will facilitate detection of cases, encourage further research on the topic and increase public awareness of potential adverse effects of agrochemicals.

EPIDEMIOLOGIC AND CLINICAL CHARACTERISTICS

The global CKD epidemic is attracting growing attention, and it is predicted to be a major contributor to disease burden in the near future.[12] The estimated prevalence of 8%–16% worldwide is likely to rise rapidly on the wave of the epidemics of diabetes and hypertension.[13] CKD without clear etiology has been described in many countries. A well-known example is Balkan endemic nephropathy in Bulgaria, Bosnia, Croatia, Romania and Serbia (formerly part of Yugoslavia), recognized in the 1950s. [14] Aristolochic acid is now considered the principal risk factor for this form of endemic nephropathy, characterized by chronic renal tubulointerstitial disease.[15] From early in the 21st century, epidemics of CKD have begun to emerge in Sri Lanka, Central America and southern Mexico.[1–8] Other regions affected include rural areas of El-Minya and Canal Governorates in Egypt, and coastal areas of Udhanam in Andhra Pradesh, India.[9,10] Most of the areas mentioned above are agricultural lands where agrochemicals are used intensively.

Most of these CKD cases without a clear etiology (CKDu) are found in adult men aged <60 years from rural areas, especially in those cultivating rice in paddies (in Sri Lanka), vegetables (in Egypt and India) and sugar cane and other crops in Central America.[1–10] In a community survey of persons aged 15–70 years in affected districts in Sri Lanka, age-standardized CKDu prevalence was 12.9% in men and 16.9% in women.[1] A community survey in El Salvador found 17.9% of the population aged ≥18 years had CKD, of whom 54.7% had no commonly found risk factors such as hypertension or diabetes.[4] Hospital-based studies in Egypt revealed that 27%–37% of end-stage renal disease was of no clear etiology.[9]

Familial clusters of CKDu observed in Sri Lanka could suggest possible inherited influences as well as environmental factors. [15,16] Prevalence rates also increase with longer duration of working in agriculture,[1] but elderly persons are less commonly affected, raising the possibility of more recent exposure to environment toxins.[1,17] Most studies show male predominance, though a recent community survey of persistent albuminuria (albumin:creatinine ratio of ≥30 mg/g) found a higher rate among women in three administrative districts in Sri Lanka with high CKDu prevalence.[1] Even in this group, more severe disease was more common in men.[1] Other risk factors for microalbuminuria include hypertension, diabetes mellitus, urinary tract infection, drinking well water in the fields, alcohol use, smoking and pesticide application in agriculture.[15,18] Some Central American studies suggest that excessive heat stress (sun exposure), high ergonomic workloads and excessive intake of fructose-containing drinks increase CKDu risk.[8]

Few studies have documented the clinical and pathological features of CKDu in detail. However, there appear to be certain common attributes that should alert clinicians to the diagnosis of what we now suggest be termed chronic agrochemical nephropathy. An early feature is asymptomatic mild-to-moderate proteinuria, without microscopic hematuria or pyuria, in middle-aged agricultural workers from CKD high-prevalence areas.[1,5,19] Urine test results are compatible with chronic interstitial nephritis, and histology has confirmed the latter even in those with minimal proteinuria. [3,16,20] Ultrasound examination shows bilateral echogenic small kidneys very early in the illness.[19] In contrast to the glomerone-

phritides, hypertension is a late feature. With advancing disease, clinical characteristics are indistinguishable from other forms of chronic renal failure.[3,5,19] Disease progression is promoted by, among other factors, hypertension, alcohol use and chewing of betel (*Piper betle,* a leaf with mild stimulant properties).[17]

EVIDENCE FOR AN ETIOLOGICAL ROLE OF AGROCHEMICALS

The evidence for agrochemicals as a main etiological factor in the current epidemic of CKDu stems from epidemiological studies, biological analyses and animal studies. The countries and regions where CKDu has been found to cluster[1–10] had centuries of traditional agricultural practices prior to the introduction of high-yield seeds, chemical fertilizers and pesticides in the 1960s, as part of the 'green revolution.'[21] Interestingly, it was only after the green revolution that a high prevalence of CKD was detected in rural farmers, suggesting a factor related to agricultural practices could be triggering this disease. Though use of agrochemicals increased globally during and since the 1960s, the situation was distinctive in many rural areas of developing countries due to pesticide overuse and incorrect methods of handling and storage.[22] This was compounded by relatively less-educated farmers who used less mechanized forms of agriculture that increased direct contact with agrochemicals.

Recently, evidence implicating agrochemicals (fertilizers, in this instance) emerged in Sri Lanka, where CKDu patients had higher urinary excretion of cadmium (with a dose-dependent association between urinary cadmium concentrations and CKDu severity) and high arsenic levels in hair.[1] Soil samples from the affected areas, food (e.g., lotus roots) and fertilizer also had excess cadmium.[1] Uptake of cadmium from soil and its concentration in food has been known since the 1970s.[23] In affected areas of Sri Lanka, there is strong circumstantial evidence that cadmium in the food chain originates in fertilizer contamination.[24] Pesticides are also implicated: case–control studies in India found a negative association between total blood levels of organochlorines and estimated glomerular filtration rate. Parameters of oxidative stress (a possible pathway of cellular damage) were also higher in those with higher concentrations of organochlorines.[25] There is also evidence that high fluoride at critical concentrations of sodium and calcium in drinking water promotes renal damage from heavy metals, thus explaining some of the geographic clusters.[26]

Histological studies in CKDu patients show a chronic interstitial nephritis, which is compatible with longterm toxin exposure.[3,20] Furthermore, animal studies demonstrate that organophosphates (e.g., diazinon and chlorpyrifos, pesticides used in cultivation of sugar cane and other crops) and cadmium (present in fertilizer) have the potential to cause renal damage and chronic interstitial nephritis.[27–29] The organochlorines (e.g., propanil, used in rice cultivation) are also known to lead to chronic interstitial nephritis in animals.[30]

Some researchers have proposed that chronic dehydration of agricultural workers due to prolonged sun exposure could be an important factor in concentrating toxins.[8] However, dehydration *per se* is unlikely to be the primary etiological factor for a number of reasons. First, Sri Lankan data show that paddy farmers who are constantly exposed to sun had a lower risk than those doing slash-and-burn (i.e., where forests or shrubs are burnt to clear land for cultivation) or vegetable plots.[1] Second, there are no previous reports of persons exposed to excessive sun or heat having a distinct renal disease. For example, steel workers exposed to high ambient temperatures are at greater risk of urolithiasis, but not chronic kidney disease.[31] Third, tubular and glomerular disease seen with other chronic states of dehydration (e.g., anorexia nervosa) is linked more to hypokalemic nephropathy than to dehydration.[32]

Another hypothesis is that chronic dehydration and heat stress compounded by osmotic damage from high intake of fructose-containing drinks could contribute to chronic renal damage.[33] Though the theory is plausible, the above set of conditions is unlikely to be a major determinant because disorders with high urinary osmolality (such as diabetes mellitus) do not lead to chronic interstitial nephritis.

RATIONALE FOR RENAMING CKDu CHRONIC AGROCHEMICAL NEPHROPATHY

The current tendency in the global literature is to name the disorder based on location (e.g., Salvadoran agricultural nephropathy, Mesoamerican epidemic nephropathy, Udhanam endemic nephropathy, and chronic tubulointerstitial disease of Central America) or its unknown pathogenesis (e.g., unknown, uncertain, nontraditional).[1–10]

However, naming the condition *chronic agrochemical nephropathy* is an improvement upon all of these, since it points more directly to the most likely trigger of the disease. Such recognition and labeling of the condition also promise to draw greater attention of clinicians, researchers, decisionmakers and the public to the potential of agrochemicals to cause renal disease, while taking cognizance of individual agrochemicals implicated as nephrotoxins. Using the term will raise awareness in the agricultural community of a distinct deadly disease related to agrochemical exposure, and hence encourage more caution in agrochemical use. Governments will be under pressure to regulate them more strictly. The term will also give confidence to clinicians to include it in differential diagnosis of CKD, and drive preventive services towards screening of high-risk groups (e.g., mass screening of agricultural workers for proteinuria).

It is arguable that use of the term *chronic agrochemical nephropathy* earlier in the epidemic might have encouraged more timely corrective response from clinicians, researchers, communities and governments. A similar sensitization and cascade effect on research and screening took place with the labeling of analgesic nephropathy. Earlier reports from Europe in the 1950s and early 1960s used the names of individual drugs as causes of interstitial nephritis (e.g., interstitial nephritis from chronic phenacetin or phenylbutazone ingestion). It was only in the mid-1960s that the term *analgesic nephropathy* began to be widely used, coinciding with an expansion in awareness and research.[34] Whether the term contributed to or reflected expanded interest (or both), at the very least, it gave instant recognition to a previously little-known cause of chronic renal disease.

FINAL CONSIDERATIONS

Naming an environmentally-induced disease can be controversial. There is a strong possibility that vested interests (particularly agrochemical manufacturers) will challenge the use of the term *chronic agrochemical nephropathy*. However, the author believes that the threshold of evidence has been reached to christen the disease with this name, and the burden of proof now lies with the industry.

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Submitted: October 16, 2013
Disclosures: This paper was written with no external sources of funding.
Approved for publication: March 4, 2014