

## Uddanam Nephropathy/Regional Nephropathy in India: Preliminary Findings and a Plea for Further Research

Even as chronic kidney disease (CKD) emerges as a global health problem, resource-constrained nations struggle to address this challenge due to the significant cost of life-sustaining long-term renal replacement therapies.<sup>1-4</sup> Recently, investigators in Central America, Southern Asia, and Egypt have reported a form of CKD among poor agricultural working communities not attributable to traditional causes such as diabetes, hypertension, primary glomerular disease, or obstructive nephropathy. Based on the geographic areas of primary reporting, it has been called Central American nephropathy, chronic tubulointerstitial kidney disease of Central America, Mesoamerican nephropathy (MeN), Salvadoran agricultural nephropathy, Sri Lankan agricultural nephropathy, and Uddanam endemic nephropathy (India).<sup>5</sup>

This wave of CKD is distinct from previously reported regional nephropathies such as Balkan nephropathy, for which specific environmental causes are believed to have been identified.<sup>6</sup> Table 1 summarizes some of the features of this new wave of regional nephropathies typically reported from hot, low-altitude, coastal or subcostal, tropical, and subtropical regions of the world.<sup>5,6</sup> There is no universally accepted definition for this clinical entity.<sup>7-12</sup> Although Sri Lankan studies have defined it on the basis of persistent urine albumin-creatinine ratio  $\geq 30$  mg/g (but excluding glomerular proteinuria) in the absence of known causes of CKD or severe hypertension,<sup>9,10</sup> a consensus definition of MeN was recently published incorporating the standard 2012 KDIGO (Kidney Disease: Improving Global Outcomes) definition of CKD when applied to inexplicable cases of CKD originating in Central America.<sup>13,14</sup>

Notwithstanding these differences, similarities in disease patterns include late presentation, a long asymptomatic phase, nonglomerular proteinuria, and the absence of hypertension in early phases of the disease prior to reduction in glomerular filtration rate, features that are typical of chronic tubulointerstitial disease and that have been validated through urinary biomarkers and renal histopathologic studies in some cases.<sup>8,9,15-18</sup> The disease appears to be more common in young male agricultural workers.<sup>8,9</sup> Although certain occupations are clearly at risk (Table 1), genetic susceptibility may also be contributory, given an association of cases with family history of CKD and disease linkage with single-nucleotide polymorphisms in the *SLC13A3* and *KCNA10* genes, as in Sri Lankan nephropathy.<sup>8,9,19,20</sup>

The cause of these regional nephropathies remains elusive to date. Data emanating from Sri Lanka indicate a significant association of CKD cases with “chena” (slash and burn) cultivation, whereas elevated urinary pesticide levels in cases and higher urinary cadmium (although not toxic) levels in both cases and controls raise the issue of environmental pollution.<sup>10</sup> Agrochemical toxicity is a prime suspect in Sri Lanka given the increasing use and hence greater physical exposure to pesticides and chemical fertilizers from modern agricultural methods.<sup>21</sup> Additionally, chemicals such as triple superphosphate have been shown to be a repository of the nephrotoxic metal cadmium contaminating cultivable soil in CKD endemic areas.<sup>21,22</sup> However, integrative studies highlight a multifactorial causation because specific gene polymorphisms have been found to be more common in cases than controls, whereas levels of nephrotoxic heavy metals such as cadmium, arsenic, and lead were not higher in cases versus controls.<sup>19</sup>

In contrast, data for MeN have highlighted issues of heat stress, salt and water depletion, and concomitant nonsteroidal anti-inflammatory drug-induced kidney damage.<sup>23,24</sup> Certain high-risk occupations such as sugarcane harvesting (which is associated with high ambient heat, long field work hours, and extreme ergonomic workloads) have been shown to cause dehydration, as reflected in significant diurnal weight loss and elevated serum and urine osmolality at the end of work hours.<sup>8,23</sup> Cyclical dehydration of this sort, when simulated in experimental animals, leads to renal tubular damage and parenchymal fibrosis due to increased intratubular fructose synthesis, fructose metabolism by fructokinase, and subsequent oxidative tissue injury.<sup>24,25</sup> In this context, hydration practices of agricultural workers in Central America using fructose-containing beverages appears contributory.<sup>23,24</sup> Recently, dehydration-induced cyclic uricosuria and hyperuricemia have been mentioned as an additional mechanism for tubular injury in MeN.<sup>26</sup>

In the 1990s, reports of endemic nephropathy started trickling in from the Southern Indian state of

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Address correspondence to Anirban Ganguli, MD, Washington Hospital Center, 110 Irving St NW, Ste 2A70, Washington DC 20010. E-mail: [ranagang77@gmail.com](mailto:ranagang77@gmail.com)

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**Table 1.** Clinicoepidemiologic Features of Major Globally Reported Regional Nephropathies in the Last Decade

	Egypt	Mesoamerican Nephropathy	Sri Lankan Nephropathy	Uddanam Nephropathy
Geographic region	El-Minia Governorate	Rural, low-altitude, and coastal regions of Nicaragua and El Salvador mainly and to some extent Costa Rica and Guatemala	Rural, North Central Province	Uddanam area in the coastal belt of Srikalulam district and 30-40 km inland in the Chimakurthy mandal of Prakasham district of the state of Andhra Pradesh, India
Epidemiology	Cross-sectional case-control study of ESRD patients on RRT <sup>7</sup> found ESRD of unknown cause in 27% of study population	Widely reported; cross-sectional community-based, and prospective cohort studies <sup>8,11,12,43</sup> ; variable prevalence based on sex and occupation	Cross-sectional community-based studies <sup>9,10,14,43</sup> ; point prevalence of CKD varies from 5.1%-16.9% in endemic region based on persistent albuminuria as diagnostic criterion	Reviewed in <sup>5,6</sup> ; CKD point prevalence in endemic area close to 50% (unpublished estimates)
Occupations affected	Farming	Sugarcane, banana, and subsistence farming; rarely from fishing and mining	Chena farming (vegetable and other crops)	Cashew nut, coconut, and rice farming
Age, y	Mean ± SD: 46 ± 13	Median range: 30-50	Mean ± SD: 39.1 ± 14.2; prevalence increases with age	All ages but generally in third to fourth decade
Sex balance	M > F	M > F (3-4:1)	Overall: F > M; CKD stages 3-4: M > F	M > F <sup>a</sup>
Clinical features	Unknown	Silent but progressive GFR decline; low-grade proteinuria (<1 g/d); nephrotic syndrome rare; urinary sediment is bland; variable progression to ESRD; limited access to RRT	Slow progressive condition with late detection due to long asymptomatic period; bland urinary sediments; generally low-grade proteinuria (<1 g/d); bilateral small kidneys; elevated urinary biomarkers of tubular damage in early disease	Proteinuria and microscopic hematuria rare <sup>a</sup>
Risk factors implicated	Rural residence; unsafe drinking water; family history of CKD; pesticide exposure; medicinal plant use	Male sex; increasing age; hypertension; family history of CKD; sugarcane, banana farming (in men only); mining/subsistence farming; NSAIDs, heavy metals and agrochemical exposure (inconsistent)	Chena farmer; family history of CKD; use of traditional medications; ayurvedic medication use; cadmium exposure; pesticide use	Male sex; increasing age; agricultural job <sup>a</sup>
Histopathologic features	Unknown	Chronic tubulointerstitial disease with secondary glomerular and vascular damage; occasional global glomerulosclerosis from possible glomerular ischemia	Chronic tubulointerstitial fibrosis with nonspecific interstitial inflammation; rare glomerular collapse and sclerosis with fibrous intimal thickening and arteriolar hyalinosis	Tubular atrophy and interstitial fibrosis mainly with secondary glomerular and vascular changes <sup>b</sup>

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NSAID, nonsteroidal anti-inflammatory drug; RRT, renal replacement therapy; SD, standard deviation.

<sup>a</sup>Unpublished data.

<sup>b</sup>Personal communication, Dr Ravi Shankar Machiraju, January 2016.

Andhra Pradesh around a coastal belt referred to as the Uddanam region in Srikakulam district and an inland region called the Chimakurthy mandal (administrative division) in Prakasham district.<sup>27,28</sup> The region is a

verdant subtropical low-altitude terrain known for coconut and cashew plantations.<sup>28</sup> Despite a lack of official statistics, the seriousness of the problem can be gauged through media reports that claim nearly 34,000

cases and 4,500 deaths have occurred in the last decade even as the state government and medical institutions struggle to provide dialysis to the underprivileged afflicted population.<sup>29</sup> Unpublished cross-sectional data from these endemic foci suggest an extremely high CKD prevalence ranging from 40% to 60%, which is nearly 3 times higher than the national CKD prevalence of 17.2%<sup>4</sup> (personal communication, Dr Ravi Shankar Machiraju, January 2016). However, it is unclear whether this represents a regional reporting bias because CKD registry reporting in India is not mandatory and CKD of unclear cause is very common, being second only to diabetic nephropathy as a cause of CKD.<sup>30</sup>

Published data for the endemic nephropathy in Southern India are very limited, with clinical reviews<sup>5,6</sup> quoting data from an unpublished abstract. The disease entity, which was previously called Uddanam endemic nephropathy, is currently referred to as Uddanam nephropathy, after a nomenclature adopted at the 2013 World Congress of Nephrology.<sup>31</sup> Although an International Society of Nephrology–funded study is currently ongoing in the endemic region, unpublished data suggest a predilection for poor agricultural workers (mainly coconut farmers) with disease onset as early as the first decade and incidence peaking around the seventh decade. As with other regional nephropathies, hypertension and diabetes were uncommonly associated with cases, whereas a long asymptomatic period, minimal proteinuria, early anemia, hyperuricemia, and the absence of peripheral edema suggest a tubulointerstitial disease process (personal communication, Dr Ravi Shankar Machiraju, January 2016).

Although the association of specific occupations with endemic nephropathy has highlighted the issue of environmental toxins and heat stress, the cause of Uddanam nephropathy is still an enigma. While chemical analyses of cultivated rice or drinking water from the endemic region have been negative, the concern of environmental pollution with organochemical pesticides and heavy metals remains because this was not assessed in these studies.<sup>28,32</sup> Of note, recent Sri Lankan studies and Western studies have raised the possibility of nephrotoxicity from pesticides.<sup>9,33</sup> This is relevant also in the Indian context because recent studies from Northern India have shown elevated urinary levels of organochlorine pesticides in patients with CKD of both known and unknown causes.<sup>34,35</sup> The nephrotoxic role of silica through the enteral route also needs to be probed given a recent cross-sectional study from a CKD endemic village in Southern India showing significantly higher silica and strontium levels in drinking water.<sup>36</sup> Typically, silica nephrotoxicity has been reported from occupational silica dust exposure and is a

secondary glomerular disease from autoimmune diseases that are promoted by silicosis, such as SLE (systemic lupus erythematosus), Goodpasture syndrome, polyarteritis nodosa, and ANCA (anti-neutrophil cytoplasmic antibody)–associated vasculitis.<sup>37,38</sup> However, this is an unlikely mechanism in Uddanam nephropathy because glomerulonephritis is not the common pathway of injury. Nonetheless, studies in experimental animals have demonstrated the development of focal tubulointerstitial nephritis when silica in the form of magnesium trisilicate was added to drinking water at levels in the higher ranges of environmental water samples.<sup>39</sup>

Lessons learned from other regional nephropathies could lead to a more focused research. For instance, given similar climatic conditions in endemic foci in India and Central America, it is necessary to explore the possibility of heat stress nephropathy. The Sri Lankan nephropathy study is notable for its methodological thoroughness involving the use of global positioning devices, various epidemiologic tools such as stratified random and hot spot (“ground zero”) sampling, and sensitive analytic techniques to measure a large number of inorganic and organic chemicals including persistent organic pollutants in a variety of biological samples to effectively delineate differences between endemic and nonendemic regions.<sup>10,40</sup> It is necessary for both governmental and nongovernmental agencies to conduct independent studies to validate and cross-check each other’s findings.<sup>41</sup> Toward this end, a conglomeration of government, researchers, and human rights activists, similar to the La Isla Foundation or the Consortium for the Epidemic of Nephropathy in Central America and Mexico (CENCAM), could help promote transparency in research agendas and essential funding for high-quality research.<sup>42</sup>

To conclude, Uddanam nephropathy is an obscure form of regional nephropathy in India affecting an indigent rural working population. Although unpublished data allude to multiple environmental and occupational risk factors, lessons learned from recent Central American and Sri Lankan studies may help direct research in elucidating the cause of this raging public health problem.

**Anirban Ganguli, MD**

Division of Nephrology, Department of Medicine  
Georgetown University/Washington Hospital Center  
Washington DC

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