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NDT Perspectives

Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants

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ABSTRACT

Increase in the prevalence of chronic kidney disease (CKD) is observed in Central America, Sri Lanka and other tropical countries. It is named chronic interstitial nephritis in agricultural communities (CINAC). CINAC is defined as a form of CKD that affects mainly young men, occasionally women. Its aetiology is not linked to diabetes, hypertension, glomerulopathies or other known causes. CINAC patients live and work in poor agricultural communities located in CINAC endemic areas with a hot tropical climate, and are exposed to toxic agrochemicals through work, by ingestion of contaminated food and water, or by inhalation. The disease is characterized by low or absent proteinuria, small kidneys with irregular contours in CKD stages 3–4 presenting tubulo-interstitial lesions and glomerulosclerosis at renal biopsy. Although the aetiology of CINAC is unclear, it appears to be multifactorial. Two hypotheses emphasizing different primary triggers have been proposed: one related to toxic exposures in the agricultural communities, the other related to heat stress with repeated episodes of dehydration heath stress and dehydration. Existing evidence supports occupational and environmental toxins as the primary trigger. The heat stress and dehydration hypothesis, however, cannot explain: why the incidence of CINAC went up along with increasing mechanization of paddy farming in the 1990s; the non-existence of CINAC in hotter northern Sri Lanka, Cuba and Myanmar where agrochemicals are sparsely used; the mosaic geographical pattern in CINAC endemic areas; the presence of CINAC among women, children and adolescents who are not exposed to the harsh working conditions; and the observed extra renal manifestations of CINAC. This indicates that heat stress and dehydration may be a contributory or even a necessary risk factor, but which is not able to cause CINAC by itself.

Keywords: chronic interstitial nephritis in agricultural communities, CINAC, dehydration, heat stress, herbicides

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem with increasing prevalence and incidence, high cost and adverse outcomes such as vascular disease and premature death. Given the limited access to health services including availability of renal replacement therapy in the low and mid income countries (LMIC), advanced stages of CKD mean death over a short time period in most cases. Well-known causative factors of CKD include mainly diabetes, hypertension and well-characterized renal syndromes [1]. In addition to these 'traditional' causes, glomerular and tubulo-interstitial diseases due to infections, nephrotoxic drugs, herbal medications, and environmental and occupational exposure to toxicants contribute substantially to CKD, particularly in LMIC.

Since the early 1990s, coinciding with a more productive and extensive exploitation of land for agriculture [2], an increase in CKD prevalence related to non-traditional risk factors primarily affecting male agricultural workers has been reported in several tropical countries: El Salvador, Nicaragua, Guatemala and Costa Rica in Central America, Sri Lanka and India in Asia, and Egypt in Africa [3, 4]. This review reflects the opinion of a group of clinical and public health academics, involved in conducting research on the problem of chronic interstitial nephritis in agricultural communities (CINAC) in the two areas where the disease is highly prevalent, i.e. Sri Lanka and Central America.

Classic presentations of CINAC in both locations are in young men, between the third and fifth decades of life, mostly agricultural workers such as: paddy farmers in Sri Lanka and India and labourers working in sugarcane or general crops in Central America. However, there are many CINAC cases among non-agricultural workers, including women and children who live in the same environment. Another important fact is that in both regions these agricultural activities are conducted at low altitudes with high humidity and temperatures characteristic of a tropical climate. Indeed, this is the type of land where rice and sugarcane has been cultivated for centuries.

Different terms have been used to describe CINAC in the medical literature: chronic kidney disease of unknown origin; chronic kidney disease of uncertain origin; chronic kidney disease of unknown aetiology; agrochemical nephropathy, etc. In some cases, the disease is named after the region or country of its origin: Central American nephropathy; Salvadoran agricultural nephropathy; Mesoamerican endemic nephropathy (MeN); chronic tubulo-interstitial kidney disease of Central America; Uddanam endemic nephropathy (India); or Sri Lankan agricultural nephropathy, etc.

Twenty years after the reporting of the first case, CINAC is the most significant public health issue in the North Central Province (NCP) in Sri Lanka with more than 60 000 estimated patients and more than 20 000 deaths annually [5, 6]. The disease is spreading at an epidemic scale to other adjacent farming areas in the Northern, Eastern, North Western and Uva provinces. The affected area covers almost one-third of the country. It is important to note that only very few patients have been reported from the Northern province of Sri Lanka, which shares similar conditions including soil, climate, agriculture and occupational patterns with the other CINAC endemic regions. The available CINAC statistics based upon hospital records show a steady increase of cases from 2000 to 2015 [7]. The underlying cause of renal failure was not identified in 82% of CKD patients seen in the renal clinic at Anuradhapura teaching hospital between 2000 and 2002 [8]. According to the NCP statistics from 2009 to 2011, aetiology is unknown in 2809 (70.2%) of the newly diagnosed CKD patients, and only 15.7% and 9.6% were diagnosed as patients with hypertension and diabetes, respectively. The male to female ratio was 2.6:1. The majority of patients with unknown aetiology (more explicit with CINAC) were already in stage 4 (40%) at presentation; 31.8 and 4.5% were respectively in stage 3 and stage 5. Patients with stage 1 and 2 accounted for only 3.4% [9]. The World Health Organization (WHO) study group (non-randomized sample) reported that the age-standardized prevalence of CINAC is slightly higher in women 16.9% [95% confidence interval (CI) 15.5–18.3] than in men 12.9% (95% CI 11.5–14.4), but noted that more advanced stages of CINAC were seen more frequently in men (stage 3, men 23.2% and women 7.4%; stage 4 men 22% and women 7.3%) [10]. This is compatible with the well-known higher prevalence of advanced stages of CKD among men as observed in many studies [11, 12].

An epidemic of CKD, not associated with the traditional risk factors, has been reported in a few coastal areas in Andhra Pradesh, South Eastern India. More than 4000 cases have already been diagnosed among paddy and coconut farmers (Dr Ganghadar, Nephrologist, Nizam's Institute Of Medical Sciences, Hyderabad, India, personal communication).

In Central America growing numbers of CKD patients and increased CKD mortality have been observed over the last two decades, particularly in Nicaragua and El Salvador. The Pan American Health Organization has reported the following CKD-specific mortality rates (per 100 000 population) in the region: Nicaragua: 42.8; El Salvador: 41.9; Guatemala: 13.6; Panama: 12.3 [13]. These figures represent four times the global CKD mortality rate, and up to 17 times when compared with the lowest CKD mortality reported in the America region. Mortality rates of CKD are three times higher in men than in women. However, in the most affected countries, El Salvador and Nicaragua, mortality in women was significantly higher than their counterparts elsewhere in the Americas.

In El Salvador farming communities, the prevalence of CKD among adults is 15–21%. In these patients, less than half have diabetes or hypertension, males predominate, and renal damage begins early in life. CKD is the fifth leading cause of death nationwide in persons aged over 18 years and the second leading cause of death overall in men. In 2009, prevalence of renal replacement therapy was 566 per million population. According to the Ministry of Health's 2011–2012 annual report in El Salvador, end-stage renal disease (CKD stages 3–5) was the third leading cause of hospital deaths in adults of both sexes, with an in-hospital case fatality rate of 12.6% [14]. Markers of kidney damage were found even in children living in agricultural communities [15]. Women, men, adolescents and children who live in these farming communities are affected, irrespective of whether they work in the fields or not.

CINAC DEFINITION

CINAC is a CKD affecting mainly young men, occasionally women and adolescents; its aetiology is not linked to diabetes, hypertension, glomerulopathies or other known causes of renal diseases. The affected subjects live and work in agricultural communities located in CINAC endemic areas with particular socio-economic-occupational determinants such as hot tropical climates with poverty, and exposure to toxic agrochemicals through work or by ingestion of contaminated food and water or by inhalation. Proteinuria is absent or low; kidneys are small with irregular contours in CKD stages 3–4 with tubulo-interstitial lesions and glomerulosclerosis at renal biopsy. However, renal biopsy is not diagnostic but contributes currently to excluding any form of progressive glomerulonephritis,

Table 1. Minimal diagnostic criteria for CINAC

eGFR	<60 mL/min/1.73 m^2
Proteinuria of tubular type[a]	Present
24 h protein excretion	Negative or trace, + positive on dipstick
Living and working place	Agricultural community in CINAC endemic area
No other known causes for CKD	Diabetes, hypertension, glomerulopathies

[a]Non-glomerular by fractional albumin excretion, β2-microglobulin/albumin ratio and/or urine protein electrophoresis. eGFR, estimated glomerular filtration rate.

amyloidosis, etc. It gives an idea of the degree of fibrosis and helps in defining the prognosis of the CKD (Table 1).

CLINICAL PROFILE

The clinical picture of CINAC identified in both Sri Lanka and El Salvador is very similar (Table 2). CINAC is a disease that progresses slowly, however at a differing pace depending on the degree of exposure to herbicides/agrochemicals and or contaminated water. The majority of patients are asymptomatic during the early stages of the disease [16]. Some of the general symptoms reported at early stages are arthralgia, asthenia, decreased libido, muscle cramps and faintishness [17]. Nocturia, dysuria, post-void dribbling, urinary hesitancy and foamy urine are also reported. These symptoms appear in CKD stage 2 and tend to increase as the disease progresses. As for markers of renal damage, the urine sediment shows no significant abnormalities. Proteinuria is rare and moderate if present and can be defined as 'tubular' since β2-microglobulin and other tubular markers are elevated in the urine. Renal function tests show polyuria accompanied by hypermagnesuria [18], hyperphosphaturia, hypernatriuria, hyperkaliuria and hypercalciuria. Serum electrolytes reflect the excess excretion observed in urine. Blood and urine osmolarity is normal. The predominant acid-base balance disorder reported is a metabolic alkalosis. Acid-base and electrolyte disorders in urine and blood begin to appear in CKD stage 2.

Renal ultrasound shows increased echogenicity, decreased cortico-medullary ratio and irregular margins at advanced stages of CKD. Renal Doppler indicates normal blood flow in renal vasculature and parenchyma. Urinary tract and bladder ultrasound does not show malignant lesions. Ultrasound of the prostate shows normal echogenicity with no malignant lesions. Blood pressure is either normal or mildly elevated. ECG is normal in almost all the patients.

CINAC patients in El Salvador have few abnormalities of the carotid and aorto-iliac arteries but have significant tibial artery abnormalities [17]. Atherosclerosis in all upper arteries was rare, becoming more evident in the lower body and peaking in tibial arteries. One hypothesis for this selective damage could be their greater exposure to occupational toxic substances. Farmers' legs, sometimes bare, are the parts that are mostly exposed to the agrochemicals during spraying. In the same study, investigators have detected sensorineural hearing loss and osteotendinous reflex disorders. Both heavy metals and organic solvents are known to cause sensorineural hearing loss [19].

PATHOGENESIS AND HISTOPATHOLOGY

The morphological pattern of CINAC is described as chronic tubulo-interstitial nephritis, in both Sri Lanka and El Salvador [20, 21]. The main findings are interstitial fibrosis and tubular atrophy with or without inflammatory monocyte infiltration. In addition, generalized sclerosis, increased glomerular size, collapse of some glomerular tufts and lesions of extra-glomerular blood vessels (such as intimal proliferation and thickening and vacuolization of the tunica media) are also observed.

In a retrospective study of 251 renal biopsies, histopathological features of the first four stages of CINAC in Sri Lanka are described [22]. The predominant feature of stage 1 disease was mild and moderate interstitial fibrosis, while most cases did not demonstrate any evidence of interstitial inflammation. Glomerular sclerosis was absent in 62.3% of the cases. Stage 2 disease had moderate interstitial fibrosis with or without mild interstitial inflammation. Stage 3 disease had moderate and severe interstitial fibrosis, moderate inflammation, tubular atrophy and some glomerulosclerosis.

More interstitial fibrosis and tubular atrophy and less glomerulo-megaly when compared with non-sugarcane agricultural workers or non-agricultural workers were observed in 46 sugarcane workers with CINAC in El Salvador [21]. Likewise, more severe tubular atrophy was seen among sugarcane workers than non-sugarcane agricultural workers, along with greater mononuclear inflammatory infiltration. Biopsy findings support the clinical observations that males and females are suffering from the same disease in both Sri Lanka and El Salvador [21, 22].

The electron microscopy (EM) in proximal tubule showed multilaminated 'myeloid' structures of different sizes, probably related to an intracellular transport mechanism and degradation of substances by lysosomes. The occurrence of 'myeloid bodies' by EM is interesting as chloroquine toxicity and other types of drugs may evoke similar lesions [23]. There were several malaria epidemics in CINAC endemic areas in both El Salvador and Sri Lanka during the 20th century. However, consumption of chloroquine in relation to CINAC has not been studied; hence, it is premature to include occurrence of 'myeloid bodies' in the definition of CINAC.

AETIOLOGY

Although the aetiology of CINAC is unclear, it appears to be multifactorial. Two aetiological hypotheses emphasizing different primary triggers have been proposed: one related to repeated and prolonged exposure to potential toxins at work, in the drinking water and the environment of the agricultural communities, while the other is related to heat stress with repeated episodes of dehydration. Many unfavourable social determinants are strongly associated with the aforementioned harmful factors. It can lead to a devastating work environment, affecting the whole body and the kidney in particular.

A study in Sri Lanka described several risk factors for CINAC: being a farmer, using pesticides, drinking well water, a family history of renal dysfunction, having taken Ayurvedic

Table 2. Comparison of CINAC in Sri Lanka and Central America

	Sri Lanka	Central America
Primarily among	Male paddy farmers, hot climate	Male sugarcane farmers, hot climate
Diabetes	No	No
Hypertension	No	No
Glomerulonephritis	No	No
Risk factors	Farmer, male sex, agrochemical exposure, drinking well water, a family history, history of snake bite	Agricultural worker, male sex, agrochemical exposure, heat stress, dehydration, agricultural work, profuse sweating during work, malaria, NSAID use
Clinical features		
Asymptomatic (early stages)	+	+
Loss of appetite	+	+
Lethargy	+	+
Backache	+	+
Insomnia	+	+
Arthralgia	+	+
Muscle ache	+	+
Cramps	+	+
Dysuria	+	+
Foamy urine	+	+
Neurological abnormalities	+	+
Sensorineural hearing loss	NI	+
Tibial artery abnormalities	NI	+
Liver enzyme level	Normal	Normal
Urinary findings		
Hyperuricosuria	+	+
Hypernatriuria	+	+
Hypermagnesuria	+	+
Hyperphosphaturia	+	+
Hypercalciuria	+	+
Proteinuria	Neg/trace, no active sediment	Neg/trace, no active sediment
β2-microglobulin, NAG, NGAL	+	+
Blood		
Hyperuricaemia	+	+
Hyponatraemia	+	+
Hypokalaemia	+	+
Imaging	Bilateral small echogenic kidneys, decreased cortico-medullary ratio, irregular margins	Bilateral small echogenic kidneys, decreased cortico-medullary ratio, irregular margins
Histopathology		
Tubulo-intestitial nephritis	+	+
Interstitial fibrosis	+	+
Tubular atrophy	+	+
Interstitial mononuclear cell infiltration	+	+
Glomerular collapse	+	+
Fibrous intimal thickening and arteriolar hyalinosis	+	+
Immunofluorescence tests	Negative	Negative

NSAID, non-steroidal anti-inflammatory drugs; NAG, N-acetyl-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

treatment and past history of snake bite [24]. A study published in 2011 found age more than 60 years, being a farmer, family history of CKD and exposure to agrochemicals were significant risk factors for CINAC [16]; a clear association with analgesic use was not found. Another study indicates elevated dietary cadmium (Cd) as a possible causative factor for the disease [25]. They reported high Cd content in lotus rhizomes, rice and tobacco, and concluded that the provisional tolerable weekly intake of Cd was high. A comparative study of rice grains from 12 countries demonstrated that the Cd content of Sri Lankan rice is high and only Bangladesh rice had a higher content [26]. The WHO research group pointed out that the risk for CINAC was increased in individuals aged more than 39 years and those engaged in vegetable cultivation. Further, they showed pesticide residues above the reference levels in 31.6% of the urine samples of CINAC patients. The detection frequency of 2,4-D, 3,5,6-trichloropyridinol, p-nitrophenol, 1-naphthol, 2-naphthol, glyphosate and aminomethylphosphonic acid (AMPA) was 33, 70, 58, 100, 100, 65 and 28% respectively in urine of CINAC patients [10]. They have also shown that the mean concentration of Cd in urine was significantly higher in those with CINAC (1.039 μg/g) compared with controls in the endemic (0.646 μg/g) and non-endemic areas (0.345 μg/g). The WHO study group found a significant dose effect relationship between the urine Cd concentration and stage of the CKD.

A study published in 2014 shows that the CINAC epidemic among farmers in the dry zone of Sri Lanka is associated with

drinking well water, drinking water from abandoned wells and with spraying glyphosate in paddy fields [27]. This study hypothesized chronic synergistic nephrotoxicity due to herbicides, heavy metals and high ionicity in the ground water, being the primary triggers, considering in addition chronic repeated dehydration as an important modulator of chemical nephrotoxicity [28]. Working for more than 6 h daily in the field standing in the sun, drinking water only from wells, consumption of less than 3 L of water per day, and having a history of malaria are factors that lead to the development of CINAC in a study performed in Medawachchiya, an endemic area in Sri Lanka [29]. A study performed in Padaviya and Medawachchiya showed that the majority of CINAC-affected villages are located downstream, far away from the reservoirs and irrigation canals [30]. In a cascade irrigation system agrochemical washout tends to accumulate downstream [31]. A low prevalence of CINAC (1.5%) is noticed among consumers of spring water, and high prevalence (7.7%) was identified among consumers of water from shallow wells in Kebitigollawa, a CINAC endemic area in Sri Lanka [9] (26). Springs wells are originate from quartzite formation, are active throughout the year and water flows continuously. Possibility of contamination of these wells from agrochemicals is low as water is coming from deep in the earth. However, water in shallow wells is stagnant and maintains a close relationship with the canal water. Low prevalence of CINAC among spring water drinkers in the endemic region of CINAC strongly favours entry of toxins via contaminated drinking water as a crucial pathway.

Certain compounds present in ground water and soil in the disease endemic area have been postulated as possible aetiological factors for CINAC. A study done in 2011 hypothesized that elevated levels of fluoride in ground water in certain areas in Sri Lanka could be associated with increasing prevalence of CINAC [32]. A recent study revealed that the numbers of CINAC patients are high where concentrations of soil vanadium are also high [33]. Ocharatoxin A, a naturally occurring fungal toxin, was also speculated to be an aetiological agent for CINAC in Sri Lanka. A study showed that it is a natural contaminant of cereals and pulses cultivated in CINAC endemic areas but the levels detected were below the toxic limits [34]. Cyanobacterial toxin was also identified as a potential nephrotoxin in the CINAC endemic areas [35]. However, contamination of ground water in shallow wells and tube wells by cyanobacterial toxin has not been reported. Further, there are no reports that CINAC is associated with urothelial malignancies as seen in Balkan endemic nephropathy (renamed aristolochic acid nephropathy); hence, aristolochic acid contamination of foods is an unlikely suspect.

Genetic susceptibility was identified as a risk factor for CINAC by using a genome-wide association study (GWAS) [36]. The GWAS yielded a genome-wide significant association with CINAC for a single nucleotide polymorphism (SNP; rs6066043; $P = 5.23 \times 10$ in quantitative trait locus analysis; $P = 3.73 \times 10$ in dichotomous analysis) in SLC13A3 (sodium-dependent dicarboxylate transporter member 3). For this SNP, a population attributable fraction was 50% and odds ratio was 2.13.

A study group working on Mesoamerican nephropathy has shown recurrent dehydration (RD) has a role in the pathogenesis of CINAC [37]. Suggested pathophysiologic mechanisms include sub-clinical rhabdomyolysis, effects of hyperuricaemia and hyperuricosuria, hyperosmolarity-induced activation of the aldose reductase-fructokinase pathway in the kidney, and vasopressin effects [38–40]. Roncal-Jimenez and others [41] pointed out that RD might cause renal injury by activation of the polyol pathway, resulting in the generation of endogenous fructose in the kidney that might subsequently induce renal injury via metabolism by fructokinase. Fructose is not nephrotoxic itself. However, after metabolized by fructokinase, it results in uric aid, nephrotoxic oxidents and inflammatory mediators. The proximal tubule is one of the major sites where fructokinase is expressed. RD results in repeated stimulation of aldose reductase with the generation of fructose in the proximal tubule, leading to tubular injury and inflammation. In certain instances fructose-containing beverages are used as a rehydration fluid by agricultural labourers. However, this should be more carefully registered in future epidemiological studies. In a recent animal experiment, pathology consistent with that of CINAC, including elevated serum creatinine, proximal tubular injury, renal inflammation and fibrosis, was observed following repeated exposure to heat-stress-induced dehydration. Interestingly, this pathology was not observed in fructokinase-deficient mice. In addition it was shown in an animal study that access to sufficient water during the dehydration period could protect the kidney [41].

IS HEAT STRESS–AND DEHYDRATION THE MAIN TRIGGER OF CINAC?

A number of solid arguments question the major role of heat stress and dehydration in the context of CINAC. The epidemic scale growth of CINAC occurred in the 1990s in Sri Lanka and Central America [3, 4] and is related to the rapid increase in the usage of agrochemicals. Sudden change in the working conditions, temperature or rainfall, however, was not observed (Table 3). In Sri Lanka, the contemporary changes in agricultural practices were in favour of reducing the physical activity and risk of dehydration. In paddy farming, preparation of the land is a labour-intensive activity that used cattle and buffaloes for centuries. The major change occurred with the introduction of a two-wheel mini-tractor in the late 1980s and early 1990s. Almost concurrently, herbicides were applied on a large scale. Sri Lankan paddy fields are not homogenous, and are located closer to villages with big trees providing shade and shelter.

The dehydration hypothesis cannot explain the mosaic pattern of geographical distribution of CINAC in Sri Lanka. Some adjacent villages to CINAC-prevalent areas do not have the disease. No epidemic of CINAC is observed in the northern part of Sri Lanka, where environmental conditions are harsher than the endemic areas in adjacent NCP. It is important to note that agrochemicals were sparsely used in the Northern Province of Sri Lanka. The government prohibited the use of these agrochemicals during the conflict from 1980 to 2009 in view of the potential of these agrochemicals being used in the production

Table 3. Comparison of agricultural practices and environmental factors in Sri Lanka and Central America

Feature	Sri Lanka	Central America (El Salvador)
Crop	Rice main season (maha) Brown millet, cowpea, maize, groundnut, sesame, vegetable in other season (yala)	Sugar cane, maize Beans, sorghum Fruits and vegetables
Land belongs to	Farmers	90 000 blocks of land divided: cooperatives, land owners
Number of days work in the field per annum	30–40 days mainly males	6 months winter cereals 6 months summer sugarcane
Average working hours per year	150–200 h	7 h per day; 200 days—1400 h
Contribution by females	Minimal work in the field, they help during planting or seeding and during harvesting (2–3 days)	15% of the women are involved in agriculture themselves
Average temperature 8 am	27°C	27°C (coast)
Average temperature 12 pm	31°C	33°C
Average temperature 6 pm	27°C	28°C
Relative humidity	min 60%—July max 80%—December	min 45%–March max 74%–September
Annual rain fall in endemic region	1250–2000 mm	1900–2000 mm
CINAC first noticed in	1994	1999
Main fertilizers used in the region	Urea, potassium chloride, triple super phosphate	Ammonia sulphate and sugarcane formulae, triple super phosphate, urea
Main herbicide used in the region	Paraquat (1980s), glyphosate (1990s and after)	Paraquat, 2,4-D, glyphosate, triazines
Main insecticide used in the region	Chlorpyrifos (organophosphate)	Methyl parathion, methamidophos (organophosphate)
Use of persistent organic pollutant pesticides (e.g. DDT)	Heavily used in anti-malaria campaign (1945–75)	Heavily used for cotton cultivation (1955–90)
Effect of mechanization	Manual workload reduced remarkably after introduction of machines (specially mini-tractor) in the early 1990s	35% reduction of work load
Natural contaminants in ground water	Fluoride, high hardness	Arsenic, high hardness

of improvised explosive devices by terrorists. Similarly, CINAC epidemics or even isolated outbreaks are not reported from Cuba and Brazil, other sugarcane-cultivating countries having similar geo-climatic factors to the Central American region. Cuba has 51 nephrology departments around the country. All of them report monthly to the National Coordinator Centre case by case where the information is processed and controlled [42]. CINAC-compatible cases have not been reported to this registry from any department. R.H. (third author) has been working for 30 years in an outpatient renal clinic in Cuba and has never seen a single CINAC patient. Further, CINAC is not reported from Myanmar, a rice-cultivating Asian country that shares similar geo-climatic factors to Sri Lanka. Myanmar farmers have not been using agrochemicals abundantly due to the economic sanctions imposed.

In Sri Lanka and El Salvador a number of studies show a chronic interstitial nephritis in woman comparable to almost all aspects of the disease observed in male agricultural workers. These women are less or almost not at all exposed to the harsh working conditions, but developed CINAC [43]. This clinical condition in woman can only be explained by non-occupational exposure to the same toxins through ingestion or inhalation since they share the same environment as their male partners working in the sugarcane industry. There are a considerable number of construction workers in Colombo, Sri Lanka and the suburbs where agriculture practices are minimal. They are exposed to more heat during daytime compared with paddy farmers in Anuradhapura; however, no CINAC is reported.

In a study of CINAC in an endemic area in Nicaragua it has been shown that school children aged 12–18 years with no prior employment history have elevated urinary biomarkers indicating tubular injury [15]. High prevalence of CKD in children and adolescents has been reported in a descriptive epidemiologic study in three agricultural regions with known high prevalence of CINAC in El Salvador [44]. This suggests the possibility of early kidney damage prior to future occupational exposure to heat stress, dehydration or agrochemicals. Therefore, nephrotoxins in drinking water or food, maternal malnutrition, genetic susceptibility or any other exposures that might be present since childhood could be aetiological factors.

All over the world there are many individuals, e.g. those working in blast furnaces, miners working deep under the ground, who are exposed to the same harsh conditions as sugarcane workers and who have never developed rapidly progressive CIN. In miners who are submitted to regular health screening programmes in Belgium, France, the UK and many other countries, including for markers of renal damage, CINAC-like diseases have never been observed.

Some patients with CINAC show neurological symptoms such as sensorineural deafness, myoclonus and positive Babinski. Doppler ultrasound shows abnormalities in tibial arteries. These extra renal manifestations are not associated with 'dehydration *per se*'. Toxic aetiology of the disease most likely explains these symptoms. In addition, dehydration stimulates the intake of contaminated water and aggravates the effects of the toxins, by increasing their concentration in the renal tubules, particularly those who undertake long work shifts, without adequate breaks and proper rehydration. In Central America the sugarcane workers are known to quench their thirst with sugary drinks and sugarcane juice. However, the

heavy metal and pesticide content of these drinks has not been analysed.

All these arguments indicate that dehydration may be a contributing or even a necessary risk factor, but is not sufficient by itself to cause CINAC. This is the same conclusion formulated at the WHO international consultation workshop on chronic kidney disease of unknown origin (CKDu) in Sri Lanka held on 27–29 April 2016 at Colombo. Considering different aspects of epidemic CKDu in Sri Lanka (comparable to CINAC), an expert committee decided 'heat stress' is probably not the most important risk factor, but is worth exploring as a contributing factor.

CONCLUSION

The differences in the incidence of CKD among patients exposed to similar environmental conditions and risk factors further support that a single agent is unlikely to be responsible for CINAC. It is more likely that a complex interaction among the proposed risk factors contributes to the eventual development of the disease. To that cascade of events are added other factors such as social determinants that make them particularly vulnerable to prior kidney damage, such as low birth weight, malaria, diabetes, hypertension, obesity, smoking, excessive alcohol consumption, and use of non-steroidal anti-inflammatory drugs and nephrotoxic medicinal plants [45].

The occupational and environmental toxins present in poverty-stricken agricultural communities in both regions present a basal risk to men, women and children who live in that environment. These toxins enter their bodies through contaminated water, food and inhalation. For males there is added exposure through spraying of pesticides without protective equipment, by inhalation and dermal absorption not only during spraying but also by working with contaminated soil and crops. That may explain why males have such a high prevalence of CINAC, and high CKD mortality rates. These observations point towards a dose–response pattern comparable to the case of aristolochic acid nephropathies [46]. Defining the disease as heat stress nephropathy without having adequate evidence, and underestimating the role of pesticides and heavy metals in this epidemic, could seriously undermine efforts to develop effective and urgently needed public health interventions for CINAC.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Murray CJ, Barber RM, Foreman KJ *et al.* Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet* 2015; 386: 2145–2191
2. Food and Agriculture Organization of the United Nations Statistics Division (FAOSTAT). http://faostat3.fao.org/browse/Q/QC/E (22 December 2015, date last accessed)
3. Weaver VM, Fadrowski JJ, Jaar BG. Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and/or occupational nephropathy? *BMC Nephrol* 2015; 16: 145
4. Jayasumana C, Gunatilake S, Senanayake P. Glyphosate, hard water and nephrotoxic metals: are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka? *Int J Environ Res Public Health* 2014; 11: 2125–2147
5. Government Medical Officer's Association of Sri Lanka, Press Release 13 November 2013
6. Ministry of Health. Data presented at the presidential task force for prevention of kidney diseases. Colombo, Sri Lanka: Presidents house; 6 June 2014
7. Data available at Renal Unit, Provincial Director's Office, North Central Province, Anuradhapura, Sri Lanka
8. Athuraliya TN, Abeysekera DT, Amerasinghe PH *et al.* Prevalence of chronic kidney disease in two tertiary care hospitals: high proportion of cases with uncertain aetiology. *Ceylon Med J* 2009; 54: 23–25
9. Jayasekara KB, Dissanayake DM, Sivakanesan R *et al.* Epidemiology of chronic kidney disease, with special emphasis on chronic kidney disease of uncertain etiology, in the north central region of Sri Lanka. *J Epidemiol* 2015; 25: 275–280
10. Jayatilake N, Mendis S, Maheepala P *et al.* Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. *BMC Nephrol* 2013; 14: 180
11. Glassock RJ. Con: thresholds to define chronic kidney disease should not be age dependent. *Nephrol Dial Transplant* 2014; 29: 774–779
12. Benghanem Gharbi M, Elseviers M, Zamd M *et al.* Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid 'over'- and 'under'-diagnosis of CKD. *Kidney Int* 2016; 89: 1363–1371
13. Pan American Health Organization. Document CE152/25 PAHO. 152nd Session of the Executive Committee. Resolution 52nd Directing Council. Chronic kidney disease in agricultural communities in Central America [Internet]. Washington, DC: Pan American Health Organization; 2013 [cited 2016 Apr 25]. 3 p. http://www.paho.org/hq/index.php?option=com_content&view=article&id=8486%3A152nd-session-of-the-executive-committee-&catid=4877%3Agbo-152nd-session-of-the-executive-committee&Itemid=39950&lang=en (16 July 2016, date last accessed)
14. Informe de Labores 2011–2012 [Internet]. San Salvador: Ministry of Health and Social Welfare (SV). 2012 [cited 2016 Jun 12]. http://www.salud.gob.sv (Spanish) (16 July 2016, date last accessed)
15. Ramírez-Rubio O, Amador JJ, Kaufman JS *et al.* Urine biomarkers of kidney injury among adolescents in Nicaragua, a region affected by an epidemic of chronic kidney disease of unknown aetiology. *Nephrol Dial Transplant* 2016; 31: 424–432
16. Athuraliya NT, Abeysekera TD, Amerasinghe PH *et al.* Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. *Kidney Int* 2011; 80: 1212–1221
17. Herrera R, Orantes CM, Almaguer M *et al.* Clinical characteristics of chronic kidney disease of nontraditional causes in Salvadoran farming communities. *MEDICC Rev* 2014; 16: 39–48
18. Noiri C, Shimizu T, Takayanagi K *et al.* Clinical significance of fractional magnesium excretion (FEMg) as a predictor of interstitial nephropathy and its correlation with conventional parameters. *Clin Exp Nephrol* 2015; 19: 1071–1078
19. Shargorodsky J, Curhan SG, Henderson E *et al.* Heavy metals exposure and hearing loss in US adolescents. *Arch Otolaryngol Head Neck Surg* 2011; 137: 1183–1189
20. Nanayakkara S, Komiya T, Ratnatunga N *et al.* Tubulointerstitial damage as the major pathological lesion in endemic chronic kidney disease among farmers in North Central Province of Sri Lanka. *Environ Health Prev Med* 2012; 17: 213–221
21. López-Marín L, Chávez Y, García XA *et al.* Histopathology of chronic kidney disease of unknown etiology in Salvadoran agricultural communities. *MEDICC Rev* 2014; 16: 49–54
22. Wijetunge S, Ratnatunga NV, Abeysekera TD *et al.* Endemic chronic kidney disease of unknown etiology in Sri Lanka: correlation of pathology with clinical stages. *Indian J Nephrol* 2015; 25: 274–280

23. Abraham R, Hendy R, Grasso P. Formation of myeloid bodies in rat liver lysosomes after chloroquine administration. *Exp Mol Pathol* 1968; 9: 212–229
24. Wanigasuriya KP, Peiris-John RJ, Wickremasinghe R *et al.* Chronic renal failure in North Central Province of Sri Lanka: an environmentally induced disease. *Trans R Soc Trop Med Hyg* 2007; 101: 1013–1017
25. Bandara JM, Senevirathna DM, Dasanayake DM *et al.* Chronic renal failure among farm families in cascade irrigation systems in Sri Lanka associated with elevated dietary cadmium levels in rice and freshwater fish (Tilapia). *Environ Geochem Health* 2008; 30: 465–478
26. Meharg AA, Norton G, Deacon C *et al.* Variation in rice cadmium related to human exposure. *Environ Sci Technol* 2013; 47: 5613–5618
27. Jayasumana C, Paranagama P, Agampodi S *et al.* Drinking well water and occupational exposure to Herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka. *Environ Health* 2015; 14: 6
28. Jayasumana C, Gunatilake S, Siribaddana S. Simultaneous exposure to multiple heavy metals and glyphosate may contribute to Sri Lankan agricultural nephropathy. *BMC Nephrol* 2015; 16: 103
29. Siriwardhana EA, Perera PA, Sivakanesan R *et al.* Dehydration and malaria augment the risk of developing chronic kidney disease in Sri Lanka. *Indian J Nephrol* 2015; 25: 146–151
30. Jayasekara JM, Dissanayake DM, Adhikari SB *et al.* Geographical distribution of chronic kidney disease of unknown origin in North Central Region of Sri Lanka. *Ceylon Med J* 2013; 58: 6–10
31. Gunatilake S, Illangasekera T. (Invited). Hydro-epidemiology of chronic kidney disease (CKD) in Sri Lanka and its similarities to the CKD epidemic in Meso-America. In: American Geophysical Union Fall Meeting, 14–18 December, San Francisco, CA, 2015
32. Chandrajith R, Dissanayake CB, Ariyarathna T *et al.* Dose-dependent Na and Ca in fluoride-rich drinking water—another major cause of chronic renal failure in tropical arid regions. *Sci Total Environ* 2011; 409: 671–675
33. Jayawardana DT, Pitawala HMTGA, Ishiga H. Geochemical evidence for the accumulation of vanadium in soils of chronic kidney disease areas in Sri Lanka. *Environ Earth Sci* 2015; 73: 5415–5424
34. Wanigasuriya KP, Peiris H, Ileperuma N *et al.* Could ochratoxin A in food commodities be the cause of chronic kidney disease in Sri Lanka? *Trans R Soc Trop Med Hyg* 2008; 102: 726–728
35. Dissananyake DM, Jayasekera JMKB, Ratnayake P *et al.* The short term effect of cyanobacterial toxin extracts on mice kidney. Proc. Peradeniya University Research Sessions, Sri Lanka. Peradeniya: University of Peradeniya, 2011; 16: 95
36. Nanayakkara S, Senevirathna S, Abeysekera T *et al.* An Integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the north central region of Sri Lanka. *J Occup Health* 2014; 56: 28–38
37. Torres C, Aragon A, Gonzalez M *et al.* Decreased kidney function of unknown cause in Nicaragua: a community-based survey. *Am J Kidney Dis* 2010; 55: 485–496
38. Paula Santos U, Zanetta DM, Terra-Filho M *et al.* Burnt sugarcane harvesting is associated with acute renal dysfunction. *Kidney Int* 2015; 87: 792–799
39. Roncal-Jimenez C, García-Trabanino R, Barregard L *et al.* Heat stress nephropathy from exercise-induced uric acid crystalluria: a perspective on Mesoamerican nephropathy. *Am J Kidney Dis* 2016; 67: 20–30
40. Roncal-Jimenez C, Lanaspa MA, Jensen T *et al.* Mechanisms by which dehydration may lead to chronic kidney disease. *Ann Nutr Metab* 2015; 66 (Suppl 3): 10–13
41. Roncal Jimenez CA, Ishimoto T, Lanaspa MA *et al.* Fructokinase activity mediates dehydration-induced renal injury. *Kidney Int* 2014; 86: 294–302
42. Almaguer M, Herrera R, Alfonzo J *et al.* Chronic kidney disease in Cuba: epidemiological studies, integral medical care, and strategies for prevention. *Ren Fail* 2006; 28: 671–676
43. Herrera Valdés R, Orantes CM, Almaguer M *et al.* Clinical characteristics of chronic kidney disease of non-traditional causes in women of agricultural communities in El Salvador. *Clin Nephrol* 2015; 83 (7 Suppl 1): 56–63
44. Orantes C, Herrera R, Almaguer M *et al.* Chronic kidney disease in children and adolescents in Salvadoran farming communities: NefroSalva Pediatric Study (2009–2011). *MEDICC Rev* 2016; 18: 15–21
45. Porter GA. Clinical relevance. In: De Broe ME, Porter GA (eds). *Clinical Nephrotoxins*. New York, NY: Springer, 2008, 3-28
46. De Broe ME. Chinese herbs nephropathy and Balkan endemic nephropathy: toward a single entity, aristolochic acid nephropathy. *Kidney Int* 2012; 81: 513–515

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