Chronic Kidney Disease of Unknown Origin – What do we know?

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Abstract
The global burden of CKD is considerable and has risen dramatically over the past 20 years. Recently, CKD of unknown origin (CKDu), a form of CKD among rural agricultural communities has been reported worldwide. There is no strong evidence for a single cause of CKDu. Basically, it is a phenotypic environmentally acquired disease with a combination of occupational and social factors. Across all geographical regions, CKDu was most frequently associated with men, middle age, snake bite, infection, and exposure to agrochemicals, heavy metals, herbal drugs, heat stress, and dietary exposures. CKDu has emerged as a challenge in certain regions of the world as there is no acceptable global definition for CKDu. There is an urgent need for health promotion at individual and community levels for early screening of risk factors and timely management. It is also important to strengthen the health service networks for a better quality of life and patient safety as well as adequate financing. Further etiological and interventional research is needed to reduce preventable regional risk factors as well as to develop proactive and comprehensive approaches to prevent and treat the disease.

Case
A 33 year old male previously healthy presented to outpatient clinic with the complaint of decreased urine output for last 4 days. Laboratory tests revealed deranged renal function (blood urea was 140 mg/dL and serum creatinine was 3.4 mg/dL) with 1 + albuminuria, no hematuria. His eGFR was 22 ml/min (by CKD-EPI equation). There was no significant history of hypertension, diabetes, glomerulonephritis or other urinary tract disease. Patient was normotensive with blood pressure of 130/85 mmHg. Patient was a farmer and had history of frequent exposure to agrochemicals and worked in excessive heat. His kidney functions were retested 3 months later. It continued to show high serum creatinine (3.6 mg/dL). Renal USG revealed bilateral small, echogenic kidneys (right kidney 7.6 × 5.1 × 4.7 cm; left kidney 8.6 × 4.2 × 4.1 cm). Renal biopsy was not performed in view of shrunken kidneys. The patient was diagnosed with CKD stage IV of unknown origin (CKDu).

Introduction
Economic development and changing lifestyle are having a significant impact on public health and thus resulting in increasing prevalence of non-communicable diseases (NCDs). Chronic Kidney Disease (CKD) is a key determinant of adverse health outcomes and is regarded as an independent risk factor for CVD events. The global burden of CKD is considerable and has risen dramatically over the past 20 years.¹ GBD 2016 report documented that CKD had rapidly moved up the ranks of causes of global deaths and is currently positioned at 11th on the list.² The estimated global crude prevalence of CKD was 147.6 million in 1990 which increased to 275.9 million cases in 2016. In the last two decades, crude mortality also doubled from 0.59 to 1.2 million.² Predominant traditional risk factors such as diabetes followed by hypertension were the leading drivers of CKD globally and contributed 50.6% and 23.3% respectively.¹,³,⁴ Recently, a form of CKD among rural agricultural communities not attributable to traditional causes (such as diabetes, hypertension, primary glomerular disease, or obstructive nephropathy) has been reported from larger studies in Central America, Southern Asia, North and West Africa and Egypt.⁵ These have been collectively termed as CKD of unknown origin or “CKD of nontraditional cause,” or “kidney disease of unknown etiology in agricultural area”. There is lack of data on true magnitude on CKDu in India. However, data from the India CKD registry revealed CKDu is the second most common underlying cause of CKD (16.0 %) after diabetic nephropathy (31.3 %).⁶ CKDu has a multifactorial etiology of different environmental and occupational exposures, such as heat stress, dehydration, agrochemicals (pesticides, herbicides, fertilizers) heavy metals (cadmium, lead, arsenic, etc.), water sources and infections. CKDu is a life-threatening due to late recognition and rapid disease progression. Early screening of etiological risk factors for CKDu is essential to reduce the mortality and morbidity due to CKD.

Definition
It is a phenotypic environmentally acquired disease rather than a pathological entity. There is no acceptable global definition for CKDu. Case ascertainment in Sri Lanka relied on persistent proteinuria (as a urine ACR ≥30 mg/g at screening and repeat sample) whereas, in Central America, both urine dipstick and serum creatinine have been used in case identification.⁷,⁹ Common characteristics across all studies include:

- Asymptomatic and progressive

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Received: 28.09.2019; Accepted: 25.03.2019
Table 1: Risk factors associated with Chronic kidney disease of unknown origin

- Water source or intake - (Ground well, tube well, tap)- Arsenic, cadmium
- Dehydration
- Extreme physical exertion
- Heat stress
- Agrochemical exposure
- Nephrotoxic drugs and traditional remedies (Aristolochic acid)
- Smoking and Alcohol
- Infections
- Snake bite
- Family history of CKD - presence of 1 degree relative with CKD
- Neighbor with CKD - at least 1 neighbor with CKD

CKD as defined by international standards.

- Absent or sub-nephrotic proteinuria
- Absence of hematuria
- Absence of a past history of diabetes, chronic or severe arterial hypertension, HIV, snake bite, glomerulonephritis or other urinary tract disease.
- Normal HBA1C (<6.5%) and
- Normal blood pressure
  - BP should be <160/100 mmHg in untreated patients
  - BP should be <140/90 mmHg on up to two antihypertensives.

Epidemiology

Various outbreaks of CKDu have occurred in the last two decades and based on the regional areas of primary reporting, it has been called Balkan endemic nephropathy (BEN) in the Balkan States, Ita–Itai nephropathy which occurred in Japan (caused by ingesting rice contaminated with cadmium), aristolochic acid nephropathy (AAN) in Taiwan, China and overseas among users of herbal medicines, Uddanam endemic nephropathy (UEN) in India, Mesoamerican nephropathy (MeN) from Central America and Sri Lanka nephropathy (SLN) or chronic kidney disease of unknown etiology (CKDu) in Sri Lanka.5,10-13 Recently, a more appropriate term, chronic interstitial nephritis in agricultural communities (CINAC), has been used.14,15 Researchers have claimed this first epidemic due to global warming.16 These outbreaks of CKDu share some common interactive features. They affect rural populations work in agriculture or other field occupations that require extenuating labor, low income, and middle-aged men are more often affected than women.12,17 Hot, low-altitude, coastal/subcostal, tropical/subtropical regions are affected predominantly. Data on CKDu from India is scarce but in comparison to other countries, it is estimated that India contributes 16% CKDu burden worldwide.8

In a recent report of CKDu from rural population of Uddanam, Andhra Pradesh, India, Tatapudi R R et al18 reported 18.23% prevalence of CKD which is 4 to 18 times higher than other reported studies. Known traditional risk factors such as persistent hypertension, diabetes and significant proteinuria were absent in 73% of patients with CKD, identified as CKDu. This is similar to CKDu reported from Sri Lanka and rural Nicaragua. However, researcher did not find any association with age, gender disparity, education, employment in agricultural fields, contact with pesticides or habits such as tobacco smoking and alcohol consumption. Therefore, they propose that there might be a new etiological factor or multiple factors responsible for Uddanam kidney disease. Thus, there is a compelling need for a cohort study for unravelling the etiology.

Risk factors

CKDu is a life-threatening disease that requires immediate attention. Predominantly it affects socially vulnerable community, primarily young male farmers from rural areas. Basically it is an environmentally acquired disease with a combination of occupational factors3 (Table 1). In a systematic review Joseph Lunyera et al19 demonstrated that environmental pollution; heavy metals (lead, cadmium, arsenic in soil), agrochemicals, heat stress and dietary exposures (rice products, fish and seafood, legumes, meats) were reported across all geographic regions. Etiological factors like family history, agrochemical use, and heavy metal exposures were reported most frequently in the south Asia region, whereas temperature and altitude were reported only in studies from the Central America area. Across all geographical regions, CKDu was most frequently associated with agricultural occupation, men, middle age, snake bite, infection and heavy metal exposure (such as cadmium, mercury, arsenic, and lead).20,21

Climate changes and rising temperature lead to increasing dehydration and cause CKDu. Furthermore, water quality (excess fluoride, sodium/calcium imbalance in water) and type of water consumed (well water versus spring water) needs to be assessed.22 Exposure to nephrotoxins such as herbal drugs and analgesics are known to play a vital role in the etiology of CKD.23 Heavy work in excessive heat, air pollutants such as tobacco smoke, exposure to agrochemicals (Such as...
organochlorines, organophosphates, glyphosate, propanil, diazinon, carbofuran, profenofos, carbaryl, etc) leads to a cascade of events. In India, Prakasham district of Andhra Pradesh, investigators reported a significantly higher level of silica and strontium in drinking water to be a possible cause of CKDu. Another study in Coastal Uddanam and Inland of Chikmurti Mandal, Andhra Pradesh reported a high prevalence of CKDu in young adult farmers involved in the cultivation of coconut, rice, jackfruit, and cashew nut because of prolonged exposure to pesticides and occupational heat exposure. The high prevalence of CKDu was among farmers growing sugarcane, banana and mining workers (dehydrated due to high ambient heat stress, longer duration of fieldwork, and extreme workloads). Genetic susceptibility and development may also be a contributory factor for CKDu. Given the limited information about CKDu in the affected areas, it is not clear that the etiology of the kidney disease is the same in all locations.

Pathogenesis

Heat stress, dehydration, and exertion have been regarded as the main causal factors for frequent episodes of subclinical AKI. Hypovolemia, hyperosmolarity, blood thickening and inflammation are the contributory factors which can activate a variety of pathways such as activation of vasopressin, activation of RAAS, and induce aldose reductase pathway in the proximal tubule (It converts glucose to fructose that is metabolized by fructokinase, leading to oxidative tissue injury) (Figure 1). Hyperuricemia and rhabdomyolysis, secondary to dehydration, contribute to tubulointerstitial damage. Proximal tubules and interstitium are affected mainly. Clinically CKDu is characterized by tubular proteinuria (β2–microglobulinuria) and the absence of hypertension and edema (Table 2). Prevention and recommendation for future

To address the issue there should be a recommendation for a more comprehensive approach and need more research. There are multifactorial involvement and no conclusive etiology, however, the hypothesized causal factors are potentially preventable. Thus, there is potential scope for intersectoral collaboration on social and environmental indicators. Health promotion at individual and community levels for early screening of risk factors and timely management. It is important to strengthen the health service networks for a better quality of life and patient safety as well as adequate financing.

• Supply clean drinking water (pipe-borne) to mitigate contributing factors that may aggravate the effect of nephrotoxins including high silica, strontium, fluoride, calcium/sodium imbalance.
• Strengthen tobacco regulations to further protect people including children from exposure to Cd through passive smoking.
• Ensure appropriate disposal of Nickel-Cadmium batteries, plastics, bottle lids.
• Regulate the use of pesticides.
• Create the awareness (public/doctors) of the danger of inappropriate use of nonsteroid analgesics.
• Health education to safeguard the health of the general population including farmers
• Provide social welfare support to affected families to control the outbreak of CKDu.
• Early detection of pre-renal dysfunction by newer biomarkers such as neutrophil gelatinase associated lipocalin, interleukin-18 (IL-18) and kidney injury molecule_1 (KIM-1).
• As CKDu is considered as an environmental disease due to global warming, interventional studies to reduce heat stress may be of great importance.

Conclusion

CKD is already emerging as a threat to global community with hypertension and diabetes forming the major etiological resources. CKDu has emerged as a challenge in certain region of the world and there is urgent need to address the issue. There is no strong evidence for a single cause; hence multiple environmental, occupational and social factors are probably involved. Further etiological and interventional research is needed to reduce preventable regional risk factors. It is necessary for both governmental and non-governmental agencies to conduct epidemiological survey studies to identify etiological factors as well as to develop proactive and comprehensive approaches to prevent and treat the disease.

References


