Chronic Kidney Disease of Unknown Etiology: Case Definition for India – A Perspective

Abstract

Chronic kidney disease of unknown etiology (CKDu) is a form of chronic kidney disease (CKD) that is prevalent in certain rural populations around the world. It is distinct by its clinicopathologic characteristics and has multifactorial etiology, being mostly linked to several environmental toxins. Although the presentation is similar in various regions across the globe, it also differs in subtle ways from region to region. In India too, there have been reports of the disease in several pockets. There is a need for a comprehensive definition to identify the cases accurately to ease clinical diagnosis and facilitate screening of populations in affected areas. This article presents the diagnostic criteria for CKDu proposed in a consensus meeting at Chennai, India, in May 2017.

Keywords: *Chronic kidney disease of unknown etiology, diagnostic criteria, India*

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Introduction

Chronic kidney disease (CKD) is an emerging public health problem of global dimensions with a reported prevalence in the range of 11%–13%.[1] The prevalence is on the rise not only in the developed countries but also in the low- and middle-income countries, although precise estimates are not clearly available from these countries. Diabetes mellitus and hypertension are the two most common drivers for CKD in most countries, while it is associated with some ill-defined causes, termed "nontraditional" in some countries.[2]

While the global community is garnering support to tackle the CKD epidemic in urban population, CKD of unknown etiology (CKDu) is being increasingly reported from isolated, predominantly rural locations in several regions across the world.[2] Particularly, CKDu has been reported from Nicaragua, El Salvador, Costa Rica, Sri Lanka, India, Egypt, and Tunisia.[2-4]

Definition

The understanding of CKDu is hindered by the lack of a precise definition encompassing all the attributes of the disease. In the clinical context, a patient is labelled as CKDu after excluding all the known causes of CKD. There are some common clinical characteristics that define CKDu and differentiate it from some of the known causes of CKD. Across locations reported globally, the disease is seen in young and middle-aged adults, mostly males who are engaged in strenuous work for their livelihood, like agriculture and manual labor. The patients have minimal or no proteinuria. CKDu patients typically are nondiabetic and have either normal blood pressure or are only mildly hypertensive.[2,5,6] The disease is progressive leading to stage 5 CKD needing renal replacement therapy over a span of several months. Kidney biopsy, performed in few patients, has revealed varying degrees of tubular atrophy and interstitial fibrosis with inflammatory cells.[7,8]

Although there is fair degree of overlap in the clinical syndrome across the global locations, there are subtle yet salient differences between the presentations in the different regions. Hence, definition for CKDu requires inclusion of clinical and laboratory criteria which are region-specific. Formulating a definition that is comprehensive and inclusive of all the components of the disease is an arduous task and a consensus has been hard to achieve across nephrology community, public health professionals, and academic

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researchers.[9] Presently, defining CKDu is a major stumbling block in research involving CKDu and appears to be the Achilles' heel.

The disease begins insidiously and there are few or no symptoms till the disease is fairly advanced. Some of the markers that can identify CKD in early stages are not easily available. With CKDu, most of the early manifestations are associated with tubular abnormalities and alterations in urinary sediment before there is clinically evident proteinuria/albuminuria or a fall in glomerular filtration rate (GFR). There are further difficulties in estimating GFR reliably, and even then by the time there is a definite fall in estimated glomerular filtration rate (eGFR), the disease would be clearly advanced and irreversible. These are some of the problems with diagnosing CKDu.[10]

Regional Variations

The clinical picture of CKDu differs in some subtle ways from region to region.[11] While men in the second or third decade are more commonly affected in Central America, men and women are equally affected in Sri Lanka, where it affects older people in the fourth or fifth decade.[5,9] Proteinuria is more prominent in Sri Lankan nephropathy. Likewise, in India too, it affects older people, but these patients have minimal or no proteinuria and normal or only mildly elevated blood pressure. Significant differences in the clinical presentation between the regions are given in Table 1.

CKDu in India

In India, CKDu was first reported from Uddanam region of Andhra Pradesh state, which includes the coastal regions of Srikakulam district and Chimakurthy Mandal in Prakasam district.[11,12] As in other epidemic sites reported globally, there are several postulates for the causation of the disease in Uddanam region. Several earlier studies which evaluated the effect of heavy metals or pesticides with CKD in this population failed to show a significant association. The study of water from different sources for trace elements and inorganic ions was carried out in the two districts and the concentrations of different inorganic chemicals were found to be within the permissible limits for drinking water.[13] Later studies revealed that silica is consistently elevated in the groundwater in this area and it is speculated that the CKD is because of direct nephrotoxicity of silica.[14,15] Strontium is another heavy metal that is found elevated in the groundwater in several villages in this region.[15] In addition, there are reports of CKDu from some regions in Maharashtra, Odisha, and Goa, though not studied to an equivalent extent.[14,16,17] Increase in ambient temperature and fall in annual rainfall over time may be additional contributory factors of the kidney disease in these regions.[14] Genetic polymorphisms in enzymes which are involved in the metabolism of organochlorine pesticides are also being studied.[18]

Case Definition for CKDu – The Indian Perspective

In the Indian context, although CKDu is being increasingly seen and reported from multiple places, the identification continues to be based on clinical judgment, by excluding other causes of CKD. The existing literature has broadly characterized the clinical traits of the patients in the epidemic region, while a clear definition to aid CKDu diagnosis as part of surveillance, epidemiological studies, and clinical trials is nonexistent. Thus, there is an

Table 1: Key similarities and differences between presentations of CKDu in various regions

Characteristics	CKDu - Central America (MeN)	CKDu Sri Lanka	CKDu India
Geographic locations	Rural, coastal regions of Nicaragua and El Salvador, other Central American countries also affected to a lesser extent	Rural, North Central Province	Rural, Uddanam area in Andhra Pradesh, Narasinghapur block in Odisha, Akola district in Maharashtra, Canacona district in Goa
Age group	20-40 years	30-50 years and older	3rd and 4th decades
Gender	M > F, 3-4:1	F > M	M > F
Occupation	Sugarcane, banana, and subsistence farming, mining	Paddy field workers and Chena farming	Coconut, cashew, and rice farming
Clinical features	Progressive fall in eGFR, proteinuria usually absent, but if seen generally <1 g/day, hematuria common, bland urine sediment, normal blood pressure, small, shrunken symmetrical kidneys	Proteinuria generally present but less than 1 g/day, but hematuria not seen; hypertension mild to moderate	Proteinuria not common, generally less than 1 g/day, mild hypertension, hyperuricemia
Postulated risk	Low altitude, strenuous work, sugarcane cutting, heat stress, NSAIDs, high consumption of sugary drinks, pesticides, leptospirosis[2]	Heavy metals - cadmium, arsenic, pesticides, glyphosate exposure, illicit liquor, hantavirus infection	Ground water consumption, silica,[14,15,17] strontium exposure,[15] lead?[16] heat stress?[14]

CKDu: Chronic kidney disease of unknown etiology; MeN: Mesoamerican Nephropathy, eGFR: Estimated glomerular filtration rate; NSAIDs: Nonsteroidal anti-inflammatory drugs

urgent need to develop a consensus of defining CKDu in the Indian context. It is imperative to clearly define criteria which could be used to aid systematic clinical, epidemiological, and surveillance studies. For this, the criteria should have high sensitivity, but the tools for the definition should be easily applicable on a large population, cheap, and must be easily available for application in field conditions. A preliminary effort was made to put together opinions of various workers in the field comprising nephrologists, epidemiologists, pathologists, and geneticists in May 2017 at Chennai under the aegis of Indian Society of Nephrology (ISN), Indian Council of Medical Research (ICMR), and Tamilnadu Kidney Research Foundation (TANKER), a Chennai-based nongovernmental organization (see annexure below).

The work groups opted to adopt a similar approach to Pan American Health Organization (PAHO) in terms of stratifying identification into suspected, possible, and definite case [Table 2]. The group proposed mandatory criteria to suspect CKDu and also criteria to exclude other known causes for other forms of CKD. The criteria are simple and can be used for surveillance or screening purposes and can be used in field studies. At the next level, a probable case of CKDu is diagnosed by abnormal eGFR and/or urinary abnormalities persisting for more than 3 months. This stage also includes exhaustive exclusion criteria which makes it more suitable for clinic-based identification of CKDu cases. At the third level are the diagnostic criteria for determining definite case of CKDu, which include application of more advanced tools such as ultrasonography and/or kidney biopsy. This level of diagnosis is more suitable for research studies and clinicopathologic studies where stringent inclusion criteria for recruitment of cases are required. Thus, the components of the definition encompass medical history and diagnostic testing including imaging, urine examination, and biopsy in a graded manner as we climb from a probable to definite case. Such a graded approach will augur well with the feasibility of implementation at various levels of the health system be it a screening camp or surveillance study or even a clinic-based evaluation, even at tertiary centers.

Table 2: Proposed case definition for chronic kidney disease of uncertain etiology in India

1. Criteria for a suspected case:
Mandatory criteria
eGFR less than 60 mL/min/1.73 m^2 by CKD-EPI formula and/or urine protein 1 plus or more by dipstick
Exclusion criteria
History of diabetes mellitus or history of antidiabetic medications/newly detected diabetes as defined by RBS >200 mg/dL*
Self-reported history of renal disease of known etiology such as polycystic kidney disease, renal stones, history suggestive of chronic glomerulonephritis, and congenital kidney disease
2. Criteria for a possible case:
Mandatory criteria
Estimated GFR less than 60 mL/min/1.73 m^2 by CKD-EPI formula and/or dipstick urine protein 1 plus or more persisting for more than 3 months (requires repeat testing after 3 months)
Exclusion criteria
Diabetes mellitus diagnosed by HBA1C >6.5% and FBS >126 mg/dL or patient on antidiabetic medications*
Any BP more than 140/90 in stage 1, 2 CKD and BP >160/100 in stage 3, 4, 5 CKD or patient requiring two or more types of antihypertensive medications for BP control
CKD documented by ultrasound examination/tests to be suggestive of renal disease of known cause (such as obstructive pathology, stones, vasculitis, lupus)
Urine protein creatinine ratio >2 g/g
Hematuria >5 red blood cells/hpf
3. Criteria for a definite case:
All criteria satisfying probable case
With
USG showing small shrunken kidneys
and/or
Kidney biopsy s/o chronic tubulo interstitial nephritis with absence of immune deposits

CKD-EPI: Chronic kidney disease Epidemiology Collaboration; eGFR: Estimated glomerular filtration rate; RBS: Random blood sugar; HBA1C: Glycosylated haemoglobin; BP: Blood pressure; CKD: Chronic kidney disease; USG: Ultrasonography. *The presence of diabetes mellitus does not preclude a person from developing CKDu in the presence of contributory etiological factors such as environmental pollutants. However, in epidemiological settings, diabetes is to be considered as an exclusion criterion, as diabetes most commonly results in diabetic nephropathy. However, an in-office diabetic patient may be considered to have CKDu if he/she has criteria satisfying 1, 2, or 3 (as described above). Clinical reasoning may be exercised in select cases

The group concluded that these criteria could be a starting point or a guide to selection of cases of CKDu for clinical and epidemiologic studies and that these criteria could be modified in time as further knowledge into the pathogenesis of the disease advanced.

Conclusion

CKDu is increasingly being recognized in certain regions in India. The condition requires further systematic studies and large-scale epidemiologic studies for elucidation of a clear pathogenetic mechanism. Definition of the disease is clearly difficult, given the various presentations in different regions and has proved to be the "Achilles' heel." Clearly much work needs to be done to unravel the mystery of this disease and needs a concerted multidisciplinary approach.

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Conflicts of interest

There are no conflicts of interest.

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Annexure

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