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CKD of Unknown Etiology (CKDu) in Sri Lanka: A Multilevel Clinical Case Definition for Surveillance and Epidemiological Studies

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Emergence of a new form of chronic kidney disease (CKD) of unknown etiology (CKDu) during the last 2 decades has resulted in considerable morbidity and mortality among the agricultural community residing in the north central region of Sri Lanka. A 3-level epidemiological case definition to identify CKDu in Sri Lanka was developed and published by the Ministry of Health in November 2016. The Sri Lanka Society of Nephrology (SLSON) refined the definition through a consensus of experts using a systematic approach in August 2017. An initial consultative meeting with the participation of 31 experts, including nephrology specialists, experts on primary care and epidemiology, and policy and university academics with long-standing experience in CKDu research, was held to identify the gaps in the existing definition. Following the meeting, a facilitator conducted 2 rounds of remote consultations using the Delphi method to obtain consensus of the participants on suggestions to improve the existing case definition. The process was initiated in August 2017 and was completed in April 2018 and resulted in the participants agreeing to a refined multilevel clinical case definition for CKDu to be used in surveillance and epidemiological studies. This article describes the process used and development of this new case definition for CKDu in Sri Lanka.

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CKD is a global health burden with a significant economic cost to health care systems worldwide. Nearly 500 million people are estimated to have CKD, of whom more than 80% are believed to be living in low- and middle-income countries (LMIC).[1] Apart from the traditional risk factors such as diabetes mellitus and hypertension, low socio-economic status, environmental factors, and low nephron mass resulting from intrauterine growth retardation predispose to CKD in these LMIC countries.[2] Emergence of hot spots of CKD confined to certain geographical locations including coastal regions of Central America, Andra Pradesh in India, northern parts of Australia, and the north central region of Sri Lanka has further escalated the economic and social impacts of the disease.[3,4] For example, according to estimates from Health Metrics and Evaluation, CKD was among the top 10 causes of age-standardized disability-adjusted life years in Latin America; CKD-attributable disability-adjusted life years doubled in this region between 1990 and 2015, and their rank as a cause of disability-adjusted life years has risen from 18th to 5th during this period. Similarly, age-adjusted death rates in the Central American countries El Salvador and Nicaragua have been significantly higher and rising compared to those of other countries in the region from 1997 to 2013.[5]

In Sri Lanka, for the year 2016, the 8th leading cause of in-hospital mortality was reported as diseases of the urinary tract under which the deaths due to CKD are reported in Sri Lanka (Annual Health Statistics, Sri Lanka, 2016). In contrast, it was the leading cause of hospital deaths in 2 districts that lie in the north central region of Sri Lanka, namely Anuradhapura and Polonnaruwa. The primary contributor to this relative high rate is the emergence of a new form of CKDu during the last 2 decades. The disease is not associated with typical risk factors for CKD such as diabetes or hypertension, and it primarily affects young and middle-aged individuals belonging to low socio-economic groups living in agricultural communities. It is progressive, is asymptomatic until the late stages, and the

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characteristic histopathology on renal biopsy is a chronic tubulointerstitial disease with secondary glomerulosclerosis.[6]

Recently, the entity CKDu has been named as chronic interstitial nephritis in agricultural communities (CINAC).[7] However, for the purposes of this paper, the term CKDu was used, as it is familiar to many and continues to be used in publications. A 3-level epidemiological case definition to identify CKDu in Sri Lanka was developed and was published by the Ministry of Health in November 2016 (Ministry of Health, Sri Lanka, 2016). It was believed that this case definition should be further refined in keeping with new evidence on the pathogenesis, clinical features, and progression of the disease that has emerged since the development of the previous definition. The Sri Lanka Society of Nephrology (SLSON) refined the definition through a consensus of experts using a systematic approach in August 2017. This paper describes the process used and development of this new case definition for CKDu in Sri Lanka.

Methods

An initial consultative meeting was convened under the auspices of SLSON in August 2017 to identify gaps in the existing definitions of CKDu based on fresh evidence. The participants invited were specialist nephrologists of SLSON, experts on primary care, epidemiology, and policy (from the Ministry of Health, the National Science Foundation [NSF], the Coordinating Secretariat for Science, Technology and Innovation [COSTI], and the World Health Organization [WHO]), and university academics with long-standing experience in CKDu research locally and with overseas collaborators (11 nephrologists, 7 university academics, and 13 other experts). Views on clinical diagnosis and management of CKD and CKDu were captured by nephrologists, recent research advances reported by university academics, and perspectives from primary care provided by experts from the Ministry of Health. Members of the WHO, NSF, and COSTI were included in view of their interest on research in CKDu and their involvement with the development of previous case definitions of CKDu.

At the consultative meeting, new research evidence was presented on demographics and clinical features of CKDu in Sri Lanka. An emphasis was on work published since the previous case definition. This was followed by a discussion on the drawbacks of the existing definition and a proposal for its modification. The consensus was to develop criteria for a 3-level clinical case definition of CKDu. The 3 levels corresponded to primary care, for epidemiologic surveillance, and for clinical diagnosis. Following the meeting, a facilitator conducted 2 rounds of remote consultations using the Delphi method to obtain consensus of the participants on the proposed criteria. This is a structured iterative process that uses a series of ''rounds'' to gather information on a particular subject from a panel of experts. It allows one to obtain, anonymously, views of a larger group of experts across diverse locations. It also avoided the domination of the process of developing a consensus by a few experts.

Additional concepts that emerged from an in-depth literature review performed by the facilitator were added to the draft before it was recirculated among the participants. It was agreed that the opinion of the majority would be considered in acceptance or rejection of the proposed. A total of 25 experts were selected for the Delphi from the participants at the consensus meeting. They included 11 nephrologists, 6 university academics, and 8 other experts. There were 2 sequential rounds of online surveys, with each round conducted over a 14-day period with approximately 4 weeks between rounds. Reminders were emailed to nonresponders approximately 10 days after the initial mailing in each round, with additional reminders at 2-week intervals after the requested submission date. Only participants who completed the initial survey round were included in the subsequent round. The results for each item in the first round were shared with the second round. The response rate was 15 of 25 (60%) in the first round and 10 of 15 (67%) during the second round.

Inclusion of a criterion required more than 50% of respondents agreeing to retain it.

The process was initiated in August 2017, was completed in April 2018, and resulted in the participants agreeing to a refined multilevel clinical case definition for CKDu to be used in surveillance and epidemiological studies.

Results

The agreed-upon final clinical case definition is based on 3 tiers of diagnosis: (i) ''suspected CKDu,'' relevant for the primary care level; (ii) ''probable CKDu,'' for epidemiologic surveillance; and (iii) ''confirmed CKDu,'' for clinical diagnosis (Table 1).

Discussion

Accurate identification of individuals affected by CKDu is the key to understanding the true burden of the disease, its geographical distribution, and associated risk factors. The new clinical case definition

Table 1. Case definition of Chronic Kidney Disease of Unknown Etiology (CKDu) Sri Lanka 2018 Update

Suspected CKDu
Essential criteria
eGFR <60 ml/min per 1.73 m^2 using CKD-EPI equation: One-time measurement using standardized methods for creatinine measurement[a]
OR albuminuria ≥ 30 mg/g creatinine[a]
OR proteinuria ≥ 150 mg/g creatinine[b]
Exclusion criteria to identify suspected CKDu among those satisfying above criteria
Urine protein: creatinine ratio > 3000 mg/g creatinine[b]
Diabetes based on self-report of diagnosis OR being on treatment OR capillary random plasma glucose ≥ 200 mg/dl[a]
Hypertension based on treatment with more than 2 drugs OR untreated blood pressure of >160/100 mm Hg (preferably using electronic blood pressure apparatus, sitting position, at least 2 readings 1 min apart)[a]
Acute kidney injury that required dialysis in the past based on the history or documented evidence[b]
Age > 70 yr[b]
Probable CKDu
Essential criteria
eGFR < 60 ml/min per 1.73 m^2 using CKD-EPI equation[a]
OR urine albumin: creatinine ratio ≥ 30 mg/g creatinine[a]
OR urine protein: creatinine ratio ≥ 150 mg/g creatinine[b]
On repeat assessment after 12 wk
AND satisfying the criteria for suspected CKDu[a]
Exclusion criteria to identify probable CKDu among those satisfying above criteria
Diabetes based on the presence of any of the standard criteria for diagnosis (fasting plasma glucose ≥126 mg/dl, 2-h plasma glucose ≥200 mg/dl on oral glucose tolerance test, HbA1c ≥6.5%)[a]
Clinical OR laboratory OR ultrasound evidence of other known causes of CKD such as • Polycystic kidney disease[a] • Congenital malformations[a] • Autoimmune diseases[a] • Glomerular diseases[a]
Ultrasound evidence of • Unequal kidney sizes with a discrepancy of >1.5 cm[b] • Obstructive nephropathy[a] • Kidney stones of any of the following features o An obstructive stone[b] o A nonobstructive single stone >10 mm[b] o A non-obstructive multiple stones >5 mm in either or both kidneys[b]
Confirmed CKDu
Confirmed with histopathology consistent with CKDu
All the above mentioned criteria for probable CKDu AND (in addition) histopathological features consistent with CKDu on biopsy[a]
Confirmed clinically in the absence of histopathology
All the above mentioned criteria for probable CKDu AND (in addition) renal biopsy not possible[b]

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKDu, chronic kidney disease of unknown etiology; eGFR, estimated glomerular filtration rate

[a]Criteria that were formulated during the consensus meeting and had 100% agreement during the first round of the Delphi process.

[b]Criteria that needed to be added or modified because of division of opinion during the first and second rounds of the Delphi process.

provides a sound scientific basis for recognition of cases of CKDu. It is simple, practical, and could be applied at different settings—suspected and probable case definition for surveillance and epidemiological studies, and confirmed case definition for the clinical setting. In addition, the format and most of its content are in keeping with case definitions developed to identify CKDu cases elsewhere in the world, thereby allowing comparisons of the data on incidence and prevalence with those of other regions and countries.[8,9]

The definition of CKDu as "suspected" and "probable" was based on the widely accepted definition of CKD established by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD workgroup.[10] The intention was to diagnose all cases of CKD rather than just CKDu alone. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was recommended in estimating GFR, as this equation has been found to be more accurate in GFR estimation in individuals with near-normal kidney function and hence is more useful in screening populations for the presence of CKD.[11]

Distinction of CKDu from other CKDs in Sri Lanka is based mainly on its relatively low proteinuria with bland urinary sediment and the scarcity of hypertension, which, when present, is usually mild. Since at least 1 study has shown that up to 20% of CKDu patients have 2+ or more albuminuria on dipstick testing, proteinuria of >3g/d was decided as the upper cut-off value for excluding CKDu.[12] Proteinuria of ≥150 mg/g creatinine was added as an optional criterion for screening for CKDu, which could be used where there are no facilities to determine urine albumin-to-creatinine ratios. It is understood that some patients with early CKDu do not have albuminuria or proteinuria and also have an estimated glomerular filtration rate (eGFR) of ≥60, but this is a problem encountered when screening for any CKD, not only CKDu.

One of the main controversies, which arose during the working group discussions, was the exclusion criterion based on the presence of diabetes and moderate-to-severe hypertension in a country where the prevalence of these 2 conditions is high. The mere presence of hypertension and diabetes does not necessarily suggest that they are the main causes of CKD unless there is evidence of other end-organ involvement. However, screening for retinopathy, neuropathy, or left ventricular hypertrophy is often not possible in the community and in primary care settings. In addition, diagnosing all patients with diabetes and moderate-to-severe hypertension who have proteinuria as suspected CKDu patients will impose an unrealistic number of cases on the CKDu case registries and exaggerate the magnitude of the problem to policy makers. Therefore, it was decided to exclude all individuals having diabetes and moderate-to-severe hypertension at the suspected and probable levels of diagnosis of CKDu. This was considered to be justified, as all diagnosed CKD cases are routinely referred to specialist clinics, and patients with diabetes and hypertension who have CKDu would be distinguished in these better-equipped clinics and eventually counted back on the CKDu databases.

Age >70 years was added as a new exclusion criterion. This was based on the known inverse association of

age with eGFR. Large cross-sectional studies of healthy individuals show a prevalence around 35% of eGFR <60 in those >70 years of age.[13] The CKD in this elderly group tends to be in the absence of traditional risk factors such as diabetes and hypertension. It is commonly nonproteinuric, as with CKDu, and is thought to be a result of age-related arteriosclerosis leading to glomerular ischemia. It was believed that the prevailing definition of CKDu without an upper age limit would overdiagnose CKDu among elderly individuals.

Acute kidney injury that required dialysis in the past based on patient history or documented evidence was also added as a new exclusion criterion. This was based on the evidence that severe AKI requiring dialysis is a strong risk factor for developing CKD.[14] Development of AKI severe enough to require dialysis is not uncommon among individuals living in the CKDu endemic area in Sri Lanka, predominantly as a result of snake bites and leptospirosis.

A new addition was the inclusion of a category of "confirmed clinical cases of CKDu in the absence of histopathology." This category was added to give due recognition to patients who have met all the criteria for probable cases of CKDu in whom a kidney biopsy was not performed (either because of small kidneys or refusal to consent).

There are several strengths in the present case definition. First, it is simple and easy to apply even in a resource-poor setting. Second, it will allow epidemiologists, researchers, and clinicians to diagnose CKDu cases at different levels with a substantial specificity. Third, because the definition is based on internationally accepted clinical and laboratory criteria, it could be used to detect and compare the true burden of CKDu across communities and regions.

One of the main limitations of this definition is the lack of a signature histopathological feature to confirm the diagnosis of CKDu. It is essentially a diagnosis of chronic tubulo-interstitial nephritis in the absence of known secondary causes. The CKD-EPI equation used for calculation of eGFR is not validated for Sri Lankans, and the urine albumin-to-creatinine ratio cut-off to diagnose CKD has been derived from populations in which the primary causes of CKD have been either diabetes or hypertension. Therefore, it is important that the present case definition be validated in communities having a high prevalence of CKDu in Sri Lanka.

The present case definition is likely to evolve as new information surfaces from clinical and epidemiological studies involving CKDu. It is crucial that an agreed-upon basic minimum primary data set, including sex, age, weight, serum creatinine, urine albumin, and other risk factors, are gathered and reported during CKD surveillance and epidemiological studies.[15]

DISCLOSURE

All the authors declared no competing interests.

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