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Chronic kidney disease of uncertain etiology in Sri Lanka: Are leptospirosis and Hantaviral infection likely causes?

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ABSTRACT

Chronic kidney disease of uncertain etiology (CKDu) has been a severe burden and a public health crisis in Sri Lanka over the past two decades. Many studies have established hypotheses to identify potential risk factors although causative agents, risk factors and etiology of this disease are still uncertain. Several studies have postulated that fungal and bacterial nephrotoxins are a possible etiological factor; however, the precise link between hypothesized risk factors and the pathogenesis of chronic kidney disease has yet to be proven in prior studies.

Leptospirosis and Hantavirus infections are important zoonotic diseases that are naturally maintained and transmitted via infected rodent populations and which present similar clinical and epidemiological features. Both infections are known to be a cause of acute kidney damage that can proceed into chronic renal failure. Several studies have reported presence of both infections in Sri Lanka. Therefore, we hypothesized that pathogenic *Leptospira* or Hantavirus are possible causative agents of acute kidney damage which eventually progresses to chronic kidney disease in Sri Lanka.

The proposed hypothesis will be evaluated by means of an observational study design. Past infection will be assessed by a cross-sectional study to detect the presence of IgG antibodies with further confirmatory testing among chronic kidney disease patients and individuals from the community in selected endemic areas compared to low prevalence areas. Identification of possible risk factors for these infections will be followed by a case-control study and causality will be further determined with a cohort study.

If the current hypothesis is true, affected communities will be subjected for medical interventions related to the disease for patient management while considering supportive therapies. Furthermore and possibly enhance their preventive and control measures to improve vector control to decrease the risk of infection.

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1. Background

Chronic kidney disease of uncertain etiology (CKDu) has been reported over the last two decades mostly concentrated in the dry zone areas of Sri Lanka since the endemic occurrence of the disease was first recognised during the 1990s [1,2]. CKD is defined as progressive kidney damage evidenced by structural and gradual decline of functional abnormalities of the kidney that becomes irreversible. It is frequently asymptomatic until the late stages of the disease [3].

There are approximately 20,000 admissions or re-admissions of patients with renal failure to government hospitals, with approximately 2000 annual deaths according to available health statistics. There are approximately 70,000 estimated CKD patients in known high risk endemic areas [4]. There is a high prevalence with increasing incidence that has reached crisis proportions in the North Central Province (NCP) which is considered the main agricultural region under reservoir-based irrigation [5,6].

Early diagnosis of the disease poses a significant challenge since CKDu symptoms often emerge slowly and appears frequently in stage 3 or 4 of the disease [7]. Pathological characteristic features of CKDu, including interstitial fibrosis, interstitial inflammation, glomerulosclerosis and tubular atrophy, were present during retrospective renal histopathological analysis carried out in Sri Lanka [3,8].

Numerous studies have established hypotheses using a variety of investigative efforts to narrow down and identify potential risk factors in recent years (Fig. 1). The origin and cause of the disease is

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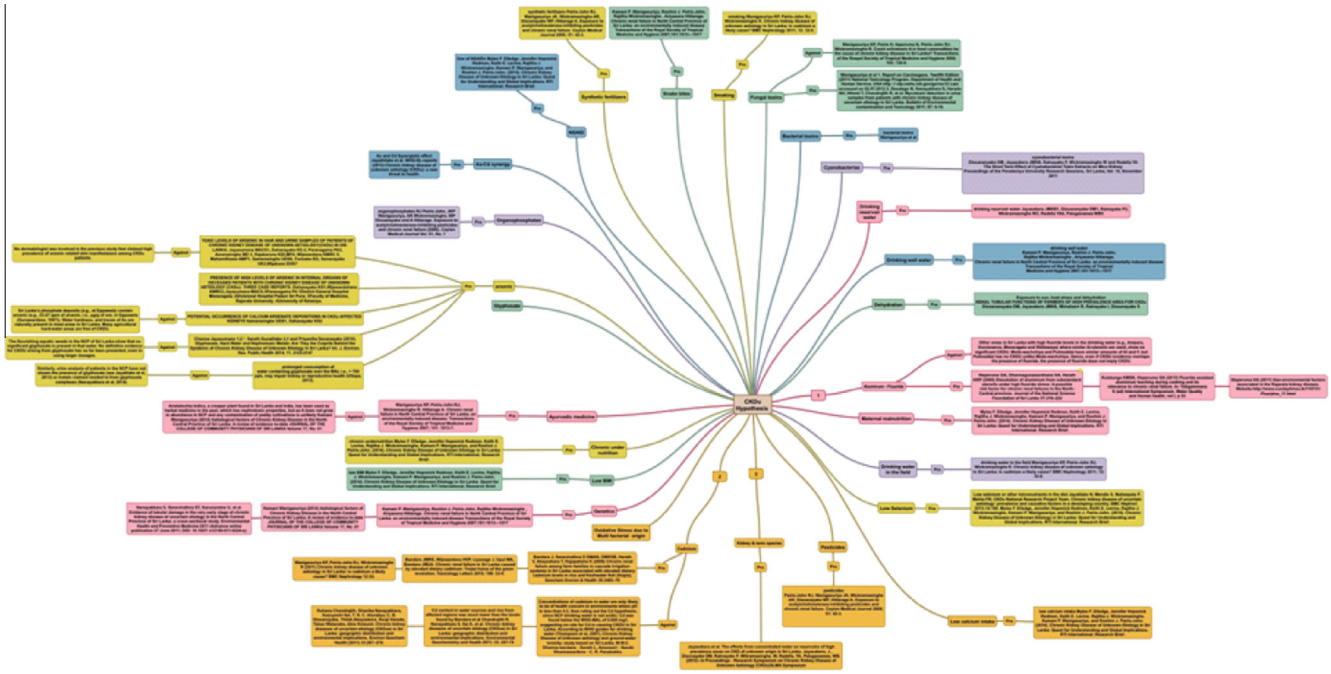

Fig. 1. Summary of established hypothesis on chronic kidney disease of uncertain etiology (CKDu) in recent past in Sri Lanka. Adopted from; The Coordinating Secretariat for Science, Technology and Innovation (COSTI), Sri Lanka (2015), Available; http://www.costi.gov.lk/index.php/en/com-dpcalendar-submenu-locations/ckdu-page (Accessed on 14th January 2016).

still unknown due to insignificant sample sizes and the use of imprecise experimental methods [9]. Most of the studies are focused on environmental factors, exposure to agrochemicals, snake bites, lifestyle, and genetic predisposition [10,11].

In Sri Lanka, a few studies have postulated that fungal and bacterial toxins present in food and drinking water in CKDu endemic areas are nephrotoxins and a possible etiological factor. A study was also carried out to find the short term nephrotoxic effects of cyanobacterial extracts isolated from stagnant water in reservoirs and canals. The possible nephrotoxin observed during the study also resulted in acute tubular necrosis (ATN) in mice when fed the extracts for over one week [12].

OchratoxinA (OA), a natural fungal toxin produced by *Penicillium* and *Aspergillus* species has nephrotoxic properties. OA levels were determined in 98 random food samples consumed in the NCP of Sri Lanka including maize (*Zea mays*) and raw and parboiled rice (*Oryzasativa*); two major cereals cultivated in the area. The OA levels were found to be lower than the recommended statutory maximum limit; therefore, OA ingestion via these foods is less likely to be a risk factor for CKDu and further studies are required [13]. A recent study determined the presence of higher urinary excretion levels of dietary contents known to be nephrotoxic such as aflatoxins (AFLs), ochratoxins (OTs) and fumonisins (FBs) in CKDu patients and their relatives living in a CKDu endemic community. However, the study needs further exposure assessment to correlate disease occurrence [14]. In all prior studies, the precise link between hypothesized risk factors and the pathogenesis of CKDu is yet to be scientifically constructed.

Several studies carried out in Nicaragua have suggested systemic infections such as leptospirosis and hantavirus as causative agents for CKDu, as they are known to cause acute kidney injury (AKI) which may progress to CKD [15,16].

Leptospirosis is considered to be the most prevalent bacterial zoonotic disease of humans and animals worldwide and is notably endemic in Sri Lanka. Over the past decades, it has been an emerging public health issue in Sri Lanka. The country's Epidemiology Unit reported the largest ever outbreak in 2008 with 7406 reported cases and more than 2500 cases were reported annually during the last five years [19]. Leptospirosis is caused by infection with pathogenic spirochetes of the genus *Leptospira* which are often transmitted to humans in close contact with livestock and poor sanitation. Moreover, it is considered as an occupational disease due to significant exposure to urine and body fluids of infected animals that enter via skin abrasions or mucous membranes [17,18]. *Leptospira* are naturally maintained in host animals as a chronic renal infection. However, the reported estimated incidence might be inaccurate as leptospirosis can easily be misdiagnosed as most reported cases are only clinically confirmed based on presenting symptoms. Leptospirosis is often characterised by fever, nausea, malaise, conjunctival hyperaemia, and jaundice, and symptoms may vary from mild to severe. Severe manifestations include pulmonary haemorrhagic events, acute kidney injury (AKI), hepatic failure, and may subsequently lead to death. The kidney is the main target organ of *Leptospira* and the immune response is involved in the development of tubulo-interstitial nephritis in infected patients [20,21].

An outbreak of leptospirosis occurred in 2011 in Anuradhapura district where Agampodi et al., carried out a cross-sectional study with 96 clinically suspected cases presenting with fever, headache and oliguria, and 32 (33.3%) were confirmed by quantitative polymerase chain reaction (qPCR) as having leptospirosis infection [22]. Of 32 confirmed cases, 7 had AKI as confirmed by serum creatinine levels. Although no laboratory diagnostic tests for other pathogens were performed for the remaining 64 clinically suspect cases, there is a possibility of a leptospirosis-like illness such as Hantaviral infection. Both leptospirosis and Hantaviral infections are likely to be clinically misdiagnosed and indistinguishable due to their similar symptoms and non-specific clinical presentation [23].

Hantavirus is an RNA virus belonging to the family *Bunyaviridae*. There are four distinct viruses that have been identified as Hantaan, Seoul, Puumala and Prospect Hill which are naturally maintained in rodent hosts as asymptomatic infections. Humans can develop either Haemorrhagic fever with renal syndrome (HFRS)

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