

Global Dimensions of Chronic Kidney Disease of Unknown Aetiology (CKDu); A Comparison Study

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Abstract:

The form of Chronic Kidney Disease (CKD) with a lacking known cause of origin unlike most other forms is said to be CKD of Unknown aetiology (CKDu). This condition has been often reported from tropical and subtropical countries around the world, specially, including Asian countries like Japan from where CKDu was first reported; and shows a growing risk of spreading around the world. Due to the absence of early signs and symptoms, CKDu is not diagnosed up until it reaches an irreversible state. Researches are being carried out to find the aetiology of the disease to help patients with better prognosis. Those have been able to put forward several hypotheses including hot climate, agricultural economy, hard water, heavy metals, microbial toxins, infectious diseases and genetic predisposition as the CKDu causatives. Also these researches have paved to identify more similarities and few differences between the CKDu cases reported from different countries. With the main aim to identify the epidemiology of CKDu in Asia, this article has been written with the intension of looking the similarities and differences of CKDu found in Asian countries. Already published primary and review articles have been studied and summarized in this article to present a review on epidemiology of CKDu in Asia.

Keywords: agrochemicals, agricultural activities, CKDu (Chronic Kidney Disease of Unknown aetiology), heavy metals, WHO (World Health Organization)

Chronic Kidney Disease of Unknown Aetiology (CKDu)

CKDu is a different form of CKDs where unlike the most others, it is not caused as a result of a prolonged abnormal health condition such as high blood pressure (hypertension), diabetes, and heavy proteinuria included primary glomerular disorders (O'Callaghan-Gordo *et al.*, 2019). Instead, it doesn't show any early signs and symptoms for its occurrence and progression, and is often reported from low income and middle income countries. More than 80% of the approximate 500 million people affected with CKDs globally are considered to be suffering from CKDu (Wijewickrama *et al.*, 2019). This condition is widely seen among rural male agricultural farmers and those that work

under heavy sun and heat for long hours (O'Callaghan-Gordo *et al.*, 2019).

Definition

With the difficulty in diagnosing CKDu that did not had a proper diagnosing criteria, "National Research Programme for CKDu" was launched in 2008 by the World Health Organization (WHO) joining with the Healthcare and Nutrition Ministry. This programme's scientific committee put forward the criteria for definition of CKDu. As of that a CKD is said to be CKDu if it does not show a past medical history of DM (diabetes mellitus), chronic/severe hypertension, glomerulonephritis, urological diseases or snake bite. Also, CKDu will have the HBA_{1c} level normal (<6.5%) and the blood pressure will be <160/100mmHg if

untreated or <140/90mmHg if treated with anti-hypertensive medications up to two (Wanigasuriya, 2012).

Signs and Symptoms

Though CKDu does not show up any signs and symptoms at early stages, it tends to appear with disease progression. Fever, tiredness, pain in joints and dysuria are seen more commonly. Headache, backache, weakness in muscles and vomiting can also be seen sometimes. Most prominent biochemical feature observed in CKDu patients is that they show an elevated level of serum creatinine. And the most prominent histopathological feature is that the kidneys are observed to be reduced in size on ultrasound images (Johnson, Wesseling and Newman, 2019).

CKDu around the World

CKDu is reported from many countries around the world including Japan like Asian countries, Egypt like African countries and El Salvador like European countries. CKDu was reported from Japan in 1912. It was then reported in 1956 from Danube region including Bulgaria, Bosnia, Croatia, Serbia and Romania. This type of CKDu is termed as Balkan endemic nephropathy (BEN). People suffering from BEN were in the age range 50-60yrs and both the genders were observed to be equally affected. Impaired concentrating capacity, tubular proteinuria, induced tubular-acidosis, decreased glomerular filtration rate and glycosuria are some observed features of BEN. With the consumption of *Aristolochia species* contaminated wheat been reported frequently as the risk factor, in 1993 it was identified as the cause of BEN (Gifford *et al.*, 2017). Mesoamerican nephropathy (MEN) is another form of CKDu reported in 2002 from El Salvador, Nicaragua, Guatemala and Costa Rica like Central American countries along the Pacific coast. Increased level of serum creatinine, muscle pain, joint pain, leukocytosis, hematuria, low-grade/ no proteinuria and hypokalemia are few clinical findings of MEN. It was observed to affect males and females in ratio $\geq 3:1$ and

the patients were reported to be in the age range 20-50yrs. Populations seen to be affected with MEN include cotton workers, sugarcane workers, corn farmers, port workers, construction workers, brick workers, shrimp farm workers, fishing industry workers and miners. Causative of MEN has not been identified up to now but areas with low altitude and hot climate, heavy physical work, dehydration, NSAIDs, heavy metals, pesticides, tobacco use, leptospirosis like infections and genetics have been hypothesized as the causes. CKDu has also been reported from Mexico, Tierra Blanca and Veracruz State rural farmers of Cantaloupe, sugarcane, rice and papaya living in hot climates. Cases have also been arise from Sudan and Southern Egypt (Johnson, Wesseling and Newman, 2019).

CKDu in Asian countries

CKDu in Japan

Japan was the first country to report CKDu cases. In 1912, people living in the Jinzu river basin reported pain in bones, weakness of muscles and kidney failure. This condition was more commonly seen among postmenopausal women. Due to the pain felt in bones by the patients suffering with this disease, it was named as "Itai-Itai" which is the saying for "ouch-ouch" in Japanese. A waddling gait, osteomalacia, tubular proteinuria and proximal tubular dysfunction were also observed in those patients. Their renal histology showed interstitial fibrosis, glomerular ischemia and tubular atrophy. With the finding of higher concentrations of Cadmium in pathology specimens of patients, rice and soil, Japan's Ministry of Health and Welfare in 1968 identified this condition as Cadmium-induced nephropathy caused due to chronic exposure to Cadmium through occupational contact, smoking or contaminated food (Gifford *et al.*, 2017).

CKDu in India

CKDu in India has been first reported in 1990s and is showing an increase in prevalence. This condition is mostly seen

among poor farmers of coconut, rice and cashew nuts who live in hot environments mainly including Central India including Andhra Pradesh, Chhattisgarh, Odisha and Maharashtra states. The patients were mostly men in the age range 30-60yrs. CKDu in India is named as Uddanam Nephropathy after a village in Andhra Pradesh where CKDu was more prominent. The causative of the disease has not been identified yet but tropical climate, low intake of water, excessive usage of painkillers and presence of Silica in groundwater are hypothesized as the causes. Patients were reported to have a low grade/ no proteinuria, a blood pressure of normal range and comparatively bland sediments of urine with infrequent red blood cells and leukocytes. Chronic interstitial disease was shown in renal biopsy (Johnson, Wesseling and Newman, 2019).

CKDu in Sri Lanka

CKDu was first reported in Sri Lanka in early 1990s from North Central Province (NCP). It has become one of the major health burdens in the country and affects mostly the socioeconomically poor male farmers engaged in paddy and chenna agriculture (Ruwanpathirana *et al.*, 2019). Apart from NCP which is the highest CKDu affected province of the country, it has been also reported from Uva province and North Western province while showing a spread into Southern province and Central province (Siriwardhana *et al.*, 2015). Male agricultural farmers in Sri Lanka of working age are the main victims of CKDu in Sri Lanka than women and children as they are the ones who work in fields. As families in Sri Lanka get their income through the earning of the male in the family and since the working age males are affected a family's income drops affecting the economy of the country. Therefore a although dialysis is the only treatment method for end-stage renal diseases, due to its cost CKDu patients are unable to afford it bringing a burden for the whole family (Elledge *et al.*, 2014). The exact cause for

CKDu in Sri Lanka has also not been identified yet but hot climate; contaminated drinking water; fluoride toxicity (Rajapakse, Shivan than and Selvarajah, 2016); use of low quality aluminum cooking utensils; excessive usage of agrochemicals; arsenic, lead, mercury and cadmium like heavy metal exposure; working for long hours in heat without taking in adequate water; microbial toxins and genetic predisposition are some hypothesized causative factors (Wanigasuriya, 2012).

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