NDT Digest

CKD of undetermined aetiology: Tens of thousands of premature deaths yet too many unknowns remain.

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Introduction

Tens of thousands of working-age adults have been dying from unexplained end-stage renal disease (ESRD) in Central America and South Asia. As the cause of this chronic kidney disease (CKD) remains unknown, this condition/these conditions (a unified aetiopathology has not been confirmed) have been termed “CKD of Undetermined Aetiology” (CKDu). “CKD of Non-Traditional Aetiology”, “Chronic Interstitial Nephritis in Agricultural Communities”, “Mesoamerican Nephropathy”, “Sri Lankan Agricultural Nephropathy” and “Uddanam Nephropathy” are also used but here we use the term CKDu.

The first reports of CKDu, almost 20 years ago, were based on observations of an excess of working-age adults from agricultural communities in El Salvador and Sri Lanka receiving dialysis, but without diagnoses explaining their ESRD[1,2]. Available population-level data now support a high prevalence of renal dysfunction in the absence of known risk factors in Central America and South Asia[3–5] but the global extent of the problem remains unclear (Figure). Lack of access to renal replacement therapy (RRT) in many affected areas means death from ESRD is common.

Definition

Although Kidney Disease Improving Global Outcomes criteria can be used to identify CKD, defining CKDu is challenging as it rests primarily on excluding known causes of disease using clinical and biochemical criteria (as imaging and histopathology are often inaccessible)[6]. The use of the term CKDu has generally been restricted to individuals with renal impairment of unknown cause from agricultural and/or socioeconomically deprived populations with a high reported prevalence of CKD (often

based on a single eGFR measure) in the absence of common identifiable aetiologies (e.g. diabetes or glomerulonephritis, as evidenced by heavy proteinuria and/or hypertension). It is not typically used to describe sporadic cases of ESRD without diagnosis in high-income countries.

Even using simple criteria identifying CKDu can be problematic as as accessing accurate eGFR testing may be difficult in many low-income settings. Furthermore, both the distribution of normal kidney function, and the validity of eGFR equations developed elsewhere, are unknown in many populations impacted by CKDu.

Clinical features

CKDu typically presents with asymptomatic renal impairment without associated hypertension or heavy proteinuria. Hyperuricaemia is prominent in established disease, and “chistata” (dysuria) is described in Central America[3]. The histological pattern is similar between regions, showing interstitial fibrosis, tubular atrophy and glomerulosclerosis without immune-complex or crystal deposition[7]. There is a male preponderance. In Central America CKDu often (but not exclusively) affects young adult sugarcane workers[3] and loss of eGFR can be dramatic[8], whereas in Sri Lanka, the condition occurs more commonly in middle-age[4].

Recently, a febrile illness with acute kidney injury (AKI) has been reported in populations at risk of CKDu in both Sri Lanka and Nicaragua[9]. Biopsies during these episodes demonstrate a non-granulomatous acute interstitial nephritis (AIN). Although some patients with this presentation progress to chronic renal impairment, there is

currently inadequate evidence that this syndrome is a necessary precursor of CKDu.

Aetiology

Candidate causes of CKDu include metabolic responses to heat/dehydration, environmental factors (agrochemicals, metals, phyto/mycotoxins), infection and drugs/alcohol but identifying causal factors in observational studies has proven challenging. There is currently insufficient evidence to support any single cause of disease, and an as yet overlooked factor may be responsible. The lead hypotheses are discussed below.

Heat/dehydration

It has been proposed that strenuous manual labour in hot conditions without adequate hydration leads to repeated tubular injury and subsequent fibrosis. Injury from heat and volume depletion could be exacerbated by myoglobin release from muscle and/or urate crystalluria and studies have demonstrated a rise in serum creatinine across a sugarcane cutting shift[10]. However, whether these changes represent creatinine generation or excretion, are transient or sustained, and/or are a marker of an underlying lack of reserve in those with pre-existing subclinical CKD is unclear. Seasonal drops in eGFR have also been proposed to support an occupational cause of disease. However, similar annual variation in kidney function is also observed in populations not at risk of CKDu.

Agrochemicals

Poisoning by pesticides (e.g. organophosphates) can lead to AKI raising the possibility of an alternative occupational cause of CKDu. Although

there is evidence from the USA that those working with agrochmicals are at increased risk of ESRD, reports from Central America have found pesticide applicators do not exhibit excess renal dysfunction[3].

Metals

A number of metals have historically been responsible for clusters of CKD, but most studies of likely candidates including cadmium, lead, and arsenic, conducted in CKDu regions, have not identified higher levels in those with renal dysfunction[3,4].

Infection

Reports of AIN in the at-risk population raises the possibility of an infective aetiology. Studies of leptospira have demonstrated no excess seropositivity in those with renal impairment in Central America. However, other organisms of known (e.g. hantavirus) or unknown (e.g. flaviviruses) nephrotropism are endemic in areas impacted by CKDu.

Management

Avoidance of nephrotoxic drugs

Although there is no evidence to support nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides) as primary causes of CKDu, use of these agents is widespread and avoidance should be advised in those with established renal dysfunction.

Allopurinol

Laboratory findings in CKDu have led to the suggestion that urate lowering may be useful in ameliorating progressive renal dysfunction. There have been no clinical trials, but allopurinol has been used in affected regions.

Water, rest, shade

Labour conditions in areas impacted by CKDu, specifically in Central America, are often brutal. Although measures to improve work conditions should obviously be supported, there is currently no evidence that such interventions prevent CKDu.

RRT

RRT provision places huge strain on health systems in affected regions. Access remains far from universal and, anecdotally, outcomes, particularly with peritoneal dialysis in Central America, are poor.

Conclusion

CKDu leads to premature loss of life at an unprecedented scale in agricultural communities in low- and middle-income countries. Such a burden of disease is unlikely to have been neglected for so long had it been occurring in high-income settings. As the cause remains unclear, only methodologically robust studies, conducted in partnership with affected communities and local investigators, will provide data on the geographical distribution, insights into pathogenesis, and a scientific basis for urgently needed preventative interventions.

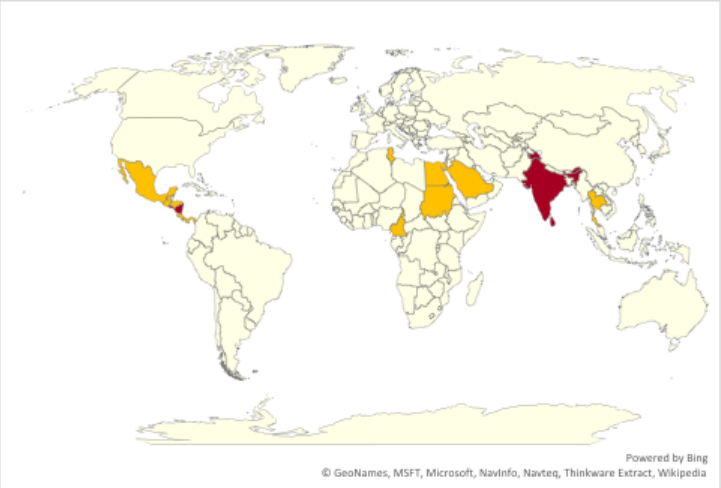

Figure: Countries affected by CKDu. Countries where there is population-based evidence of CKDu (red) are in Central America (Pacific coastal regions of El Salvador and Nicaragua) and South Asia (north central Sri Lanka and northern coastal Andhra Pradesh in southern India). There have also been reports of CKDu (gold) in Cameroon, Costa Rica, Egypt, Guatemala, Honduras, Mexico, Panama, Saudi Arabia, Sudan, Thailand and Tunisia.

References

1. Garcia Trabanino R, Aguilar R, Reyes Silva C *et al.* Nefropatía terminal en pacientes de un hospital de referencia en El Salvador. *Rev Panam Salud Publica* 2002, DOI: 10.1590/S1020-49892002000900009.
2. Lanerolle R, Kudalugoda Arachchi J, Nanayakkara S. Demographic characteristics of end stage renal disease in Sri Lanka. *J Ceylon Coll Physicians* 2000;**33**:3.
3. Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: The case for a mesoamerican nephropathy. *Am J Kidney Dis* 2014;**63**:506–20.
4. Wanigasuriya K. Update on Uncertain Etiology of Chronic Kidney Disease in Sri Lanka ' s North-Central Dry Zone. *MEDICC Rev* 2014, DOI: 10.2188/jea.JE20110082.
5. O'Callaghan C, Shivashankar R, Anand S *et al.* Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data analysis of three population-based cross-sectional studies. *BMJ* Open; 2019, In Press.
6. Caplin B, Wang C-W, Anand S *et al.* The International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology: report of the working group on approaches to population-level detection strategies and recommendations for a minimum dataset. *Kidney International*; 2019, In Press.
7. Wijkström J, Leiva R, Elinder CG *et al.* Clinical and pathological characterization of mesoamerican nephropathy: A new kidney disease in central america. *Am J Kidney Dis* 2013; DOI: 10.1053/j.ajkd.2013.05.019.
8. González-Quiroz M, Smpokou E, Silverwood R, *et al.* Decline in Kidney Function among Apparently Healthy Young Adults at Risk of

Mesoamerican Nephropathy. *J Am Soc Neprol* 2018; **29**:2200-2212
9. Fischer RSB, Vangala C, Truong L *et al.* Early detection of acute tubulointerstitial nephritis in the genesis of Mesoamerican nephropathy. *Kidney Int* 2018;**93**:753–60.
10. García-Trabanino R, Jarquín E, Wesseling C *et al.* Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador - A cross-shift study of workers at risk of Mesoamerican nephropathy. *Environ Res* 2015;**142**:746–55.