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Editorial

Mesoamerican nephropathy: a neglected tropical disease with an infectious etiology?

Abstract

An outbreak of unexplained and severe kidney disease, "Mesoamerican Nephropathy," in mostly young, male sugar cane workers emerged in Central America in the late 1990's. As a result, an estimated 20,000 individuals have died, to date. Unfortunately, and with great consequence to human life, the etiology of the outbreak has yet to be identified. The sugarcane fields in Chichigalpa, Chinandega, Nicaragua, have been involved in the outbreak, and during our initial investigation, we interviewed case patients who experienced fever, nausea and vomiting, arthralgia, myalgia, headache, neck and back pain, weakness, and paresthesia at the onset of acute kidney disease. We also observed a heavy infestation of rodents, particularly of Sigmodon species, in the sugarcane fields. We hypothesize that infectious pathogens are being shed through the urine and feces of these rodents, and workers are exposed to these pathogens during the process of cultivating and harvesting sugarcane. In this paper, we will discuss the epidemic in the Chichigalpa area, potential pathogens responsible for Mesoamerican Nephropathy, and steps needed in order to diagnose, treat, and prevent future cases from occurring.

Keywords: Mesoamerican nephropathy; Chronic kidney disease of unknown etiology, CKDu; Acute interstitial nephritis; Acute kidney injury; Nicaragua; Sugarcane; Leptospirosis; Hantavirus

A large and unrelenting epidemic of unexplained acute kidney injury (AKI) is ongoing in Central America. Substantial morbidity and mortality are associated with the epidemic, and progression of disease is rapid, from onset of acute febrile illness to renal pathology consistent with chronic kidney disease (CKD) [1,2]. Furthermore, risk factors traditionally known to cause kidney disease, including diabetes and hypertension, are not evident [3,4]. Because of surveillance system limitations, the actual burden of disease is unknown; however, the estimated number of deaths to date is in excess of 20,000 [5]. Due to the unusually high number and unexplained nature of illness and death, Central America has recently gained international attention and been designated a *CKD hotspot* [6–8]. Despite the duration and impact of this epidemic, the etiology remains unknown [3,5,7,11,12]. Thus, in 2013, The Pan American Health Organization (PAHO/WHO) issued a resolution calling for fortified disease surveillance and highlighting the urgent need for research to discover the underlying cause [8]. Based on both anecdotal evidence and published reports, Nicaragua and El Salvador bear a disproportionate burden of disease and now rank among countries with the highest kidney-related mortality in the world [5,7]. In Nicaragua, the disease primarily affects young men from poor, rural areas, the majority of whom are agricultural workers [13,14].

In April of 2014, we were invited by a large (more than 10,000 workers) sugar estate in Nicaragua to investigate the epidemic occurring among workers of their sugarcane fields near Chichigalpa, Chinandega. The Chinandega area is one of the most heavily affected in Nicaragua and where the CKD mortality rate has more than doubled since the epidemic began [14]. The San Antonio mill is one of the industries in the region that has facilitated external access to occupational health records and statistical data, contributing substantially to the information required to investigate this regional health problem. There, we met with local physicians and made environmental observations of the sugarcane fields and work practices. During our discussions, we also met with five affected workers and learned that three of them presented with a febrile illness at the time they were diagnosed with AKI, accompanied by nausea and vomiting, arthralgia, myalgia, headache, back and neck pain, weakness, and paresthesia. While no rash was reported, some workers reported a burning and tingling sensation in the skin all over the body, referred to as 'fogazo del cuerpo'. All information from

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workers was collected anonymously for hypothesis generating purposes; therefore, no consent was given. During our visits to the fields, we observed arid, hot environmental conditions and aerosolization of dirt and dust during the cane cutting process. All workers reported bringing water from home to drink in the field and were provided an electrolyte drink throughout their work shift to prevent dehydration—a practice introduced in 2002 following reports that the epidemic of renal disease could be related to dehydration and heat stress. We observed some workers rinsing their hands with water from irrigation canals and eating meals in the fields during the work day. Additionally, heavy infestations of rodent populations, predominantly *Sigmodon* species, were present.

With de-identified, aggregate surveillance data provided by the preventive health office at the private sugar estate hospital, we created an epidemic curve of acute kidney injury cases newly diagnosed from 1996 through 2013 (see Fig. 1). It was apparent from the curve that the outbreak began in 1998, peaked in 2001, and then established an endemic cycle, with increases in cases seen in 2007 and 2010. We believe this pattern fits what would be expected when a new pathogen is introduced into a naive population – an initial exposure and amplification phase, followed by the establishment of endemic transmission and subsequent periodic epidemics. Interestingly, the peaks on the curve correlate with the El Niño-southern oscillation (ENSO) weather patterns over those years [15]. In the United States, hantavirus follows a similar weather-related pattern, with peaks in rodent populations and amplification of virus transmission coinciding with heavy ENSO precipitation events [16,17]. Similarly, leptospirosis outbreaks are associated with periods of heavy precipitation and extreme weather events in tropical regions, including Nicaragua [18–20].

In light of the ecological and epidemiologic evidence – specifically, the arid environment during the harvest seasons, the dense rodent populations in the sugarcane fields, constant exposure of workers to soil and run-off water in the fields, the epidemic curve, and the clinical picture described by both clinicians and workers – our immediate concern is that a rodent-borne pathogen is responsible for the epidemic of acute renal disease, with conditions favorable for leptospirosis, hantavirus, or even a new pathogen.

Leptospirosis is a bacterial infection that can cause hemorrhagic fever with pulmonary, liver, and kidney manifestations, including acute renal failure [21]. Left untreated or inadequately treated, kidney involvement presenting as acute interstitial nephritis can progress to chronic kidney disease [22]. More than 250 serovars from *Leptospira* species are pathogenic, with new serovars still being described, and incidence is highest in tropical areas [23–25]. In the sugar estate, run-off water from the fields, to which we observed workers were exposed, is likely contaminated with urine from rodents in the fields and could be a transmission source for *Leptospira*. Interestingly, we found that workers in irrigation and drainage, as well as shrimp farmers, at the sugar estate had the highest attack rates of disease compared to other occupations, including cane cutters (see Table 1), and both occupations require constant contact with water. This is key, as *Leptospira* can be acquired through direct contact with contaminated water, through breaks in the skin, contact with mucous membranes, or by ingestion [26].

In 1995, a severe outbreak of leptospirosis occurred in Nicaragua, with the highest number of cases reported from Achuapa and El Sauce. Both of these towns are close in proximity to the sugar estate in Chichigalpa (less than 120 km). A total of 2252 cases, including 48 deaths, were identified, and a new serovar of *Leptospira* was detected

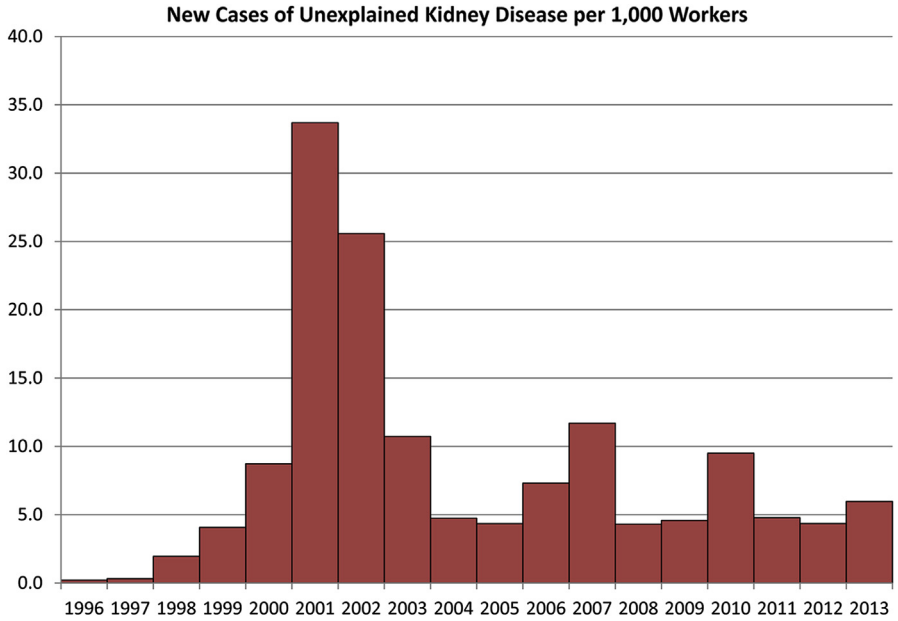

Fig. 1. Epidemic curve of new cases of unexplained kidney disease, per 1000 workers, at a sugar estate in Chichigalpa, Nicaragua, identified between 1996 and 2013.

Table 1
Attack rates per 1000 workers by occupation at a large sugar estate in Chichigalpa, Nicaragua, 2010–2014.

Occupation	Attack rate per 1000 workers
Shrimp farm worker	109.1
Irrigation and drainage worker	61.8
Cane collector/harvester	35.7
Cane cutter	35.5
Weed control worker	34.0
All other occupations	11.7

during the investigation [27]. The outbreak was most likely related to increased exposure to run-off flood waters during the rainy season [28]. Interestingly, 81 (43%) of 185 kidney specimens from rodents collected during that outbreak were found to be positive for *Leptospira* by fluorescent antibody testing. Subsequent outbreaks of leptospirosis occurred in Nicaragua in 2007 and 2010, with cases being concentrated along the Pacific coastal region of the country, spanning from Managua to Chinandega. One theory as to the geographic predilection of leptospirosis infections to the coastal lowlands relates to the soil type found in this region [20,25]. This region contains soil originating from volcanic lava and ash, which is more alkaline and allows for better water absorption and retention, thus providing an ideal environment for survival of *Leptospira*. While the outbreaks in 2007 and 2010 were similar to the outbreak in 1995, in terms of the majority of cases being diagnosed during the rainy season, it is important to note that cases in the 2007 outbreak in León were identified in February, during the dry season. It is plausible that agricultural workers having extensive contact with contaminated soil and water run-off in the irrigation ditches around the fields during the dry season could have an increased risk of exposure [29]. *Leptospira* is a plausible etiology that warrants immediate investigation in this region of Nicaragua. The evidence highlights the importance of surveillance for *Leptospira* in both the field rodents and acutely ill workers who present with renal disease.

As an alternative hypothesis, an Old World species of hantavirus, newly introduced into the rodent population in Nicaragua in the 1990's, could also explain the outbreak and ongoing transmission of acute kidney injury associated with a febrile illness. In 1993, a hantavirus outbreak occurred in the "Four Corners" region of the United States, and as part of this investigation, 1696 rodents were collected and tested in order to identify which species was the reservoir. Researchers implicated the deer mouse, *Peromyscus maniculatus*, when 30% of them were found positive for the sin nombre virus, a newly identified New World hantavirus strain that causes severe pulmonary disease [30]. In a separate study in Florida, 12% of 1500 rodents tested positive for hantavirus, and, interestingly, 95% of positive rodents were *Sigmodon* species, the same species we identified in the sugarcane fields in Nicaragua [31]. Human cases of hantavirus pulmonary syndrome have been reported in both North and South America, and reports of Old World hantavirus in the Americas is not uncommon [32–36]. A recent study in New Orleans found 3.4% of 178 brown rats were positive for Seoul virus, a hantavirus strain known to cause hemorrhagic fever with renal syndrome, lending to the possibility that this type of virus could also be circulating among rodents in Central America, including Nicaragua. To date, more than 30 strains of hantavirus have been isolated throughout the Americas, with novel hantaviruses still being identified [36–39]. While numerous studies have focused on identifying reservoirs and isolating virus, hantavirus diversity in Central America is still not well described. Since hantavirus disease can manifest as a renal syndrome similar to what is being described in the Nicaragua epidemic, it is another plausible etiology that deserves immediate scrutiny in both human cases and rodent reservoirs.

Based on our observations and review of available surveillance data from the hospital, we hypothesize that the outbreak of unexplained acute renal failure among the sugarcane workers in the region is infectious in nature. Hantavirus and leptospirosis are both pathogens that could explain the clinical picture of AKI, often accompanied by fever at onset; however, we should also consider the possibility of a new pathogen. We recommend testing human specimens (acute and convalescent serum and urine) and rodent specimens (serum, urine, and tissue), as well as soil and water samples from fields where cases were known to work, using both traditional diagnostic and novel pathogen discovery methods, for evidence of a pathogen that could explain the observed clinical scenario. In addition, the acute clinical disease picture needs to be detailed through careful retrospective review of medical data on case patients. This piece of information is critical for the development of an accurate clinical case definition, which can be used to prospectively identify individuals with acute kidney disease. From prospectively identified incident cases, data on exposures and medical history can be gathered, and biologic specimens can be collected for acute phase diagnostic testing. Finally, a case–control study would aid in accurately pinpointing the etiology of disease and most likely source of transmission. By employing an agent-host-environment approach, researchers may be able to link clinical human cases with pathogens circulating in the rodent populations with which workers are in contact, document a transmission cycle consistent with environmental evidence, describe the clinical presentation associated with infection, and accurately and quickly diagnose acute cases.

1. Conclusion

Despite the fact that the epidemic of unexplained kidney disease in young Central Americans was identified two decades ago, the etiology remains unknown. The high morbidity and mortality associated with this epidemic requires immediate attention. As of yet, very few investigators have entertained the idea of an infectious etiology. We believe that, by employing an epidemiologic approach that investigates all three elements of the agent-host-environment disease model,

we will be able to identify factors putting sugarcane workers at the greatest risk of acute kidney disease and to ascertain where the disease cycle could be interrupted, allowing the opportunity to prevent disease. It will be critical to describe the clinical features of acute phase illness in infected workers so that we can recommend intervention and prevention strategies, such as screening tools for early diagnosis, exposure reduction techniques, and treatment plans to ameliorate the pathology associated with this epidemic of kidney disease.

Conflict of interest

Two of the authors are employees of the sugar estate described in this report. There are no other conflicts of interest.

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