

An epidemic outbreak of Mesoamerican nephropathy in Nicaragua linked to nickel toxicity

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For more than 20 years, an epidemic of chronic kidney disease (CKD) of unknown origin has severely affected specific coastal communities along South America's Pacific coastline from Mexico to Panama leading

to more than 50,000 deaths. The condition, known as Mesoamerican Nephropathy (MeN), has a perplexing clinical presentation. Unlike traditional forms of CKD, it affects healthy young working-age individuals who do not have other traditional risk factors for kidney disease, such as diabetes or hypertension. The underlying cause of this devastating public health crisis has remained a mystery.

A 'CSI-style' scientific investigation led by Dr. Kristy Murray, professor of pediatrics, immunology and microbiology at Baylor College of Medicine and Texas Children's Hospital, revealed evidence for nickel toxicity as the underlying cause of this [disease](#) in a Nicaraguan "hotspot," which is among the worst-hit areas in the continent. The study provides new, compelling evidence that low-dose exposure to nickel can cause systemic inflammation, anemia and kidney injury—hallmarks of acute MeN that progresses to chronic [kidney disease](#) in around 90% of the patients. The study appeared in *PLoS ONE* this week.

"A few years back, based on my reputation of investigating many new outbreaks and my laboratory's expertise in studying tropical medicine and infectious diseases among [vulnerable populations](#), we were called to investigate the possible causes of this horrific epidemic that plagued vulnerable agricultural areas in the Pacific lowlands for decades," Murray, who is also the assistant Dean at the National School of Tropical Medicine Baylor College of Medicine and Vice Chair for Research in the Department of Pediatrics at Texas Children's, said. She initially received her outbreak experience twenty years ago at the CDC as part of the elite group of disease detectives known as the Epidemic Intelligence Service.

Although agricultural toxins were proposed as a possible factor, based on the prevalence of this disease only in specific coastal populations, the team ruled it out. Genetic mutations, as the sole cause, were also excluded because of the relatively recent emergence of this disease (in

decades versus centuries, which is typical of inherited genetic disorders) and a sharp increase in cases in the region.

"Although it was thought to be a chronic condition, after we reviewed hundreds of clinical records and conducted surveillance for new cases, we were struck by the acute 'flu-like' presentation in the initial stages of this disease. At the onset, the disease looked remarkably like a classic hyper-inflammatory response to an infection. So, we screened for several pathogens but could not pin it down to any particular infectious agent," Murray said. "We then turned our attention to clinical and pathological tests that led us to the most important clues to crack this case. Majority of the affected individuals had recently developed anemia and their kidney biopsies showed extreme inflammation in the tubules and cortico-medullary junctions of the kidney, indicative of heavy metal or trace element toxicity. The pieces of the puzzle were finally coming together."

Dr. Rebecca Fischer, who was Dr. Murray's postdoctoral fellow at the time and now assistant professor of Epidemiology at Texas A&M University, worked to pull together these complex analyses, and nephrologists, Drs. Sreedhar Mandayam and Chandan Vangala at Baylor College, helped to guide the team in their clinical interpretation of acute cases.

The team then collaborated with Drs. Jason Unrine and Wayne Sanderson at the University of Kentucky who specialize in trace element toxicity. Since the easiest way to test the levels of heavy metals is through toenails, they collected toenail clippings of individuals about three months after they experienced an acute kidney injury event and analyzed them for 15 trace elements, including heavy metals. Most importantly, they compared these analyzes to controls they recruited from the same population who had no evidence of kidney disease. They found affected cases to have significantly increased levels of nickel.

They also identified higher levels of aluminum and vanadium in affected cases than control subjects, but nickel was by far the strongest correlate, and biologically, it made sense with the clinical presentation.

Nickel is an abundant, naturally occurring heavy metal and like iron, it is essential for the human body, but is needed only in very trace quantities. Excess recurrent exposure to nickel, by incidental ingestion through contaminated water, food or soil, can cause several toxic and carcinogenic effects. Since people who work a lot with soil such as agricultural field laborers, miners and brick-makers were found to have the highest risk of acquiring this disease, the researchers theorize their source of the nickel exposure was likely geologic in nature and possibly linked to a volcanic chain in the area that became active in the late 90s, after which incidences of this [chronic kidney disease](#) began to skyrocket in lowland areas downstream from the volcanoes in this chain.

"While we still need to validate these findings in other areas impacted by MeN, such as El Salvador or Guatemala, and to confirm the geologic source of nickel contamination, we are very excited to have found a strong lead in this challenging public health problem. Based on this study, several public health strategies were implemented, such as finding ways to protect drinking water sources from soil and runoff water contamination and educating community members about the need to frequently wash their hands after working with soil. It is gratifying to see our efforts are starting to pay off. After these measures were put in place, we noticed a dramatic reduction in the number of new cases, an indication that we are moving in the right direction. This is the first-ever downward trend in this outbreak since its emergence two decades ago. Considering the sobering death toll in the affected communities, I am relieved we can finally do something about it," Murray shared.

More information: Rebecca S. B. Fischer et al, Evidence of nickel and other trace elements and their relationship to clinical findings in

acute Mesoamerican Nephropathy: A case-control analysis, *PLOS ONE* (2020). [DOI: 10.1371/journal.pone.0240988](https://doi.org/10.1371/journal.pone.0240988)

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