

# Urinary Findings Among Adults and Children in a Region of Nicaragua Endemic for Mesoamerican Nephropathy



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## INTRODUCTION

Mesoamerican endemic nephropathy (MeN), a form of chronic kidney disease (CKD) of unknown etiology, is occurring in epidemic proportions in Central America. MeN disproportionately affects young agricultural-working males without traditional risk factors for kidney disease.

The pathogenesis of MeN is unclear. Proposed mechanisms include chronic volume depletion, agrochemical or heavy metal toxic exposure, infection, rhabdomyolysis, and several others.<sup>1</sup> Multiple factors may contribute to the disease. MeN presents with an acute syndrome of acute kidney injury, leukocytosis, leukocyturia, and elevated inflammatory markers.<sup>2</sup> Clinical features include bland urinary sediment, elevated serum creatinine level, increased uric acid level, anemia, and hypokalemia.<sup>1</sup> On biopsy, the early stages of the disease reveal tubulointerstitial nephritis, whereas later stages reveal tubular atrophy, chronic glomerular changes, and interstitial damage.<sup>1,3</sup> Recent data suggest that early clinical markers might predict progression to CKD.<sup>4</sup> Awaiting changes in filtration-based markers, such as creatinine, likely results in delayed diagnosis.

Little is known on kidney function in the community-at-large in regions where MeN occurs, and data in children are especially sparse. The Pacific

lowland area of Nicaragua is a region heavily affected by MeN and where reported mortality owing to the epidemic has more than quadrupled since its emergence 2 decades ago.<sup>5</sup> The purpose of this study was to characterize urinary characteristics of both adults and children residing in communities at high risk of MeN. In this study, urine was analyzed from residents of rural northwest Nicaragua participating in community health fairs. The methods are described in the [Supplementary Material](#).

## RESULTS

Urine specimens from 471 residents, aged 3 months to 89 years, in 4 rural agricultural communities were analyzed ([Table 1](#)). Almost half of the urine specimens (44.9%) were collected on children ([Table 1](#)).

Dipstick and microscopy data are summarized in [Table 1](#) and [Figure 1](#). Tubular epithelial cells were noted in 11.0% of the specimens. Crystalluria was common, whereas proteinuria was rare. Microscopic hematuria occurred in 8.9%. On dipstick, 13.4% was positive for hemoglobin. When correlating these results, there were 8 individuals (1.7%) who were dipstick positive for hemoglobinuria but lacked red blood cells on microscopy, suggestive of rhabdomyolysis.

Leukocytes were observed in almost all specimens (99.2%); 21.2% had >5 leukocytes per field and 2.8%

**Table 1.** Children and adult urine dipstick and microscopy results

Urinary characteristic	Children n = 210 (mean [range/ SD] or %[n])	Adults n = 257 (mean [range/SD] or %[n])	P value
Median age (yr)	9 (3 mo–17 yr)	37 (18–89 yr)	
Specific gravity	1019	1019	0.87
pH	6.16	6.11	0.49
Proteinuria (% positive for any protein)	2.7	2.7	0.89
Hemoglobinuria (%)	6.7	19.1	<0.001
Nitrates (%)	0.5	2.3	0.10
Leukocytes (%)	4.3	8.2	0.09
Renal cells (%)	2.7	3.9	0.55
Uric acid crystals (%)	15.7	23.0	0.50
Phosphate crystals (%)	11.4	7.4	0.13
Leukocytes on microscopy (cells per field)	4.25	5.67	0.0054
Erythrocytes on microscopy (cells per field)	1	2	0.0081

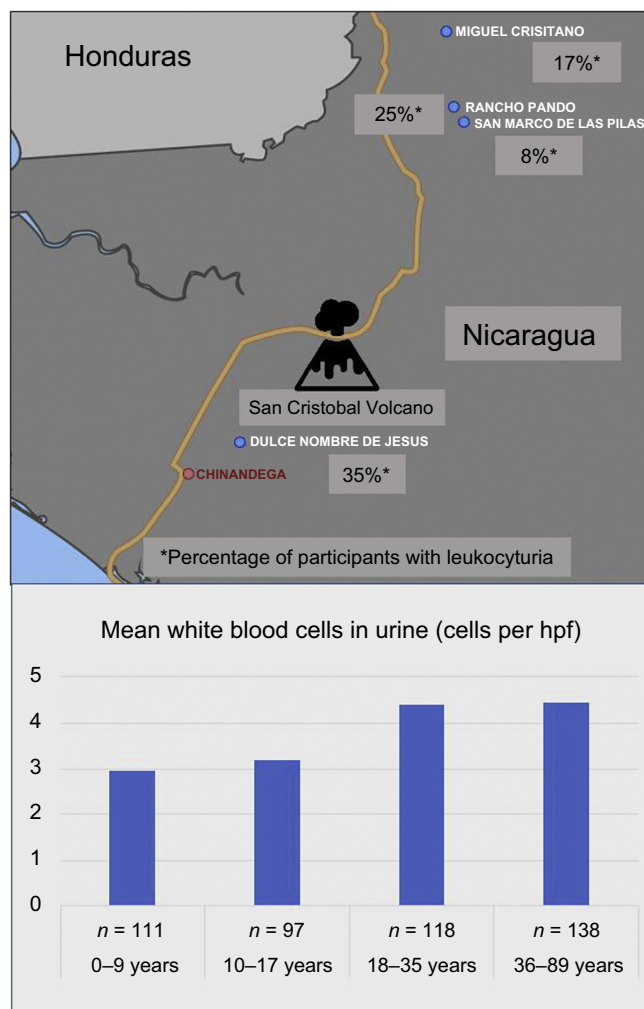
had  $\geq 30$  per field. The prevalence of leukocyturia ( $>5$  leukocytes per field) differed by community ( $P < 0.001$ ), ranging from 8.4% in San Marcos to 35.0% in Dulce Nombre de Jesus, which is located in the agricultural area considered hyperendemic for MeN (Figure 1).<sup>6</sup> Adults (24.8%) were more likely to have evidence of leukocyturia than children (17.1%) ( $P = 0.044$ ) (Table 1). Leukocytes were described as grouped in 2.8% of specimens, and none were labeled as casts.

We observed significantly greater leukocyturia with older age (average lifetime increase of 0.05 cells per field [95% CI 0.01–0.09] per 1 year of age;  $P = 0.008$  by linear regression). Nevertheless, closer examination revealed that this was driven by a particular age group: there was a per-year increase in white cell shedding of 0.29 (95% CI 0.04–0.53) cells per field ( $P = 0.021$ ) in those aged 12 to 33 years (Figure 1).

## DISCUSSION

Previously, MeN was characterized as a chronic tubulointerstitial disease with glomerulosclerosis.<sup>1</sup> Nevertheless, biopsies taken from later stages of MeN may not reflect the initial pathologic process and could reflect CKD from other causes. Fischer *et al.*<sup>3</sup> evaluated renal tissue from patients with acute kidney injury and systemic inflammation who were at the onset of MeN. Infiltration of immune cells was noted in all cases, and all had both acute and chronic components of tubulointerstitial nephritis.<sup>3</sup> Leukocyturia was common (82%).<sup>2</sup> This supports that an inflammatory agent, such as an agrochemical, heavy metal, drug, or infection, is initially driving the pathology of MeN.

In this analysis, leukocyturia was remarkably common (99.2%). This is elevated compared with previously reported sterile pyuria prevalence of 30% in a CKD population.<sup>7</sup> The prevalence of leukocyturia that increases



**Figure 1.** Sites of participating communities in northwest Nicaragua including the percentage of participants with leukocyturia by site and mean white blood cells in urine by age category. Map adapted from Heather Aleman, Amigos for Christ. hpf, high power field.

with age could suggest systemic inflammation that increases over the lifespan, such as repetitive exposure to a contaminated water source or exposure to different environmental components through occupations held by adults. Other factors affecting susceptibility, such as nutrition or immune status, may vary by age.

Importantly, we observed that adolescents and young adults had the most marked increase in leukocyturia per year. This could be related to an occupational exposure. We also found marked leukocyturia in children, a significant finding, particularly given the robust sample size of children in this analysis. There could be inflammation in young adults and children—ages when early genesis of MeN is already thought to be underway. Leukocyturia was previously found to be less common in patients who progress from acute kidney injury to CKD among MeN cases.<sup>4</sup> A study in Sri Lanka where a similar CKD of unknown etiology is prevalent revealed that 9% of children had albuminuria.<sup>8</sup> This supports that children in endemic regions

for CKD of unknown etiology undergo early kidney damage that could be detected by urine tests.

Recurrent rhabdomyolysis in the setting of labor is an etiologic theory of MeN.<sup>2</sup> In our study, <2% of this population had urinary parameters suggestive of rhabdomyolysis. In addition, urine specific gravity did not suggest severe volume depletion. We presume that participants, who were attending health fairs, were not actively working at the time of specimen collection. Thus, we may not have detected rhabdomyolysis or volume depletion that would have occurred during a normal workday.

It is possible that early systemic inflammation and thus leukocyturia could serve as a surrogate marker for kidney pathology. If so, MeN could be inexpensively detected in the early stage of kidney injury that may go unnoticed by assessing functional markers of filtration. Research should focus on identifying the cause of MeN and then implementing preventive efforts.

There are several limitations. First, this is a cross-sectional study; therefore, there were no experimental variables or interventions performed, and so caution must be taken in attributing causality. There was no control group to determine whether these findings are unique to this region. No serum creatinine was collected, so it is unknown whether participants had confirmed MeN or CKD. Also, because this was a community-based study, not all participants were employed in agriculture or performed manual labor. Participants attended the health fair voluntarily, which could lead to self-selection bias. Finally, no information on the sex of participants was collected and no differential was performed on the leukocytes. The strengths of this study include the large quantity of data points in adults and children for urinary studies in a region where it is difficult to obtain this information.

In conclusion, this cohort consisted of men, women, and children from communities located in MeN hotspots in northwestern Nicaragua. The high prevalence of leukocyturia, especially in adults compared with children, could support environmental exposures causing inflammation leading to reduced kidney function. This study also suggests that it could be beneficial to screen patients for readily available urinary biomarkers (i.e., leukocyturia) in high-risk areas, which could lead to earlier detection and better outcomes. Awareness of risk factors and early detection remain the most useful tools for ameliorating the impact of MeN until its etiology can be definitively determined.

## DISCLOSURE

KM receives compensation from the Nicaragua Sugar Estates, Ltd., to serve on a scientific advisory board

for research into Mesoamerican endemic nephropathy in agricultural workers. This board, nor its affiliation, played no role in this study. AS has been a long-term volunteer and donor to the nonprofit, Amigos for Christ. Her mother is an employee of the organization. There was no coercion or financial benefit for the author, the author's family, or the nonprofit related to this study.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Methods.

STROBE Statement.

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