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Original article

Acute kidney injury in rural workers: An environmental-stress nephropathy

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Abstract

Introduction: Mesoamerican nephropathy is a tubule-interstitial nephropathy whose etiology is still unknown. However, clinical cases like Mesoamerican nephropathy have been described in other geographically distant and ethnically diverse regions. Still, they all have a common factor: the intensity of heat and rural physical labor.

Keywords: Acute kidney injury, chronic interstitial nephritis of agricultural communities (CINAC), Mesoamerican nephropathy.

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Objective: To study whether this entity could occur among rural workers in a non-Mesoamerican region with similar climatic and working conditions, in the Colombian Caribbean countryside, and to consider how much repetitive dehydration could weigh in its pathogenesis.
Methodology: An observational study was carried out, based on field work in a farm in Sitio Nuevo (Colombia) with 28 rural worker volunteers (rice fields), who were measured for weight, blood pressure, and blood and urine samples to measure electrolytes and osmolarity, at 2 times of the day (morning and evening).
Results: Of the 28 young men workers evaluated, 5 (18 %) presented a significant increase in serum creatinine during the day (0.8±0.15 vs 1.2±0.17, p<0.001). The volume of water ingested by the workers was highly variable (2,861 ± 1,591 cc). There was a significant increase in serum sodium (p<0.001), and urinary osmolarity (p=0.01) values between morning and afternoon values in these 5 patients.
Conclusions: Eighteen percent (18 %) of the workers evaluated developed parameters compatible with acute kidney injury and dehydration during the workday in the Colombian Caribbean countryside.

Lesión renal aguda en trabajadores rurales: una nefropatía por estrés ambiental

Resumen

Introducción: la nefropatía mesoamericana es una nefropatía túbulo-intersticial cuya etiología aún se desconoce. Sin embargo, se han descrito casos clínicos similares a esta en otras regiones geográficamente distantes y étnicamente diversas. Aun así, todos tienen un factor común: la intensidad del calor y el trabajo físico rural.
Objetivo: estudiar si esta entidad podría presentarse entre trabajadores rurales de una región no mesoamericana con condiciones climáticas y laborales similares, en el campo del Caribe colombiano y considerar cuánto podría pesar en su patogénesis la deshidratación repetitiva.
Materiales y metodología: se realizó un estudio observacional, basado en un trabajo de campo en una finca de Sitio Nuevo (Colombia) en 28 voluntarios trabajadores rurales (arrozales), a quienes se les tomó peso, presión arterial y muestras de sangre y orina para medir electrolitos y osmolaridad, en 2 momentos del día (mañana y tarde).
Resultados: de los 28 trabajadores jóvenes evaluados, 5 (18 %) presentaron aumento significativo de la creatinina sérica durante el día (0,8±0,15 vs 1,2±0,17, p<0,001). El volumen de agua ingerido por los trabajadores fue muy variable (2.861 ± 1.591 cc). Hubo un aumento significativo en los valores de sodio sérico (p<0,001) y osmolaridad urinaria (p=0,01) entre los valores de la mañana y la tarde en estos 5 pacientes.
Conclusión: el dieciocho por ciento de los trabajadores evaluados desarrolló parámetros compatibles con daño renal agudo y deshidratación durante la jornada laboral en el campo del Caribe colombiano.

Palabras clave: lesión renal aguda, nefritis intersticial crónica de comunidades agrícolas (CINAC), nefropatía mesoamericana.

Introduction

Mesoamerican nephropathy (MeN) is a form of chronic kidney disease (CKD) of unknown etiology originally described in Central America, where this condition represents an important cause of morbidity and mortality [1]. MeN is suspected to be a multifactorial disease, consequently, several inducing factors have been proposed; including heat stress (severe dehydration), excessive physical work (rhabdomyolysis), environmental toxins (agrochemicals, heavy metals, aristolochic acid), infections (leptospirosis, hantavirus), nephrotoxic drugs (NSAIDs) and genetic predisposition (familial nephropathy) [1–4].

MeN has been documented mainly in workers who perform intense physical work in hot and humid conditions, and areas at lower altitudes (<500 m above sea level), such as sugar cane workers. This nephropathy is characterized by a tubular-interstitial CKD which generally presents anemia, low levels of serum electrolytes (hyponatraemia, hypokalemia, hypomagnesemia), hyperuricemia, aseptic dysuria (crystalluria with uric acid) and mildly altered urinalysis [1, 3].

This disease has also been found in other areas of the globe, geographically distant and ethnically diverse from Mesoamerica, such as Sri Lanka, Egypt, Udhanam (India), etc. Still, all of them had settings of hard physical work under high-heat climatic conditions as a common factor. Because of this, a more appropriate term for this condition has been proposed; CINAC (chronic interstitial nephritis in agricultural communities) [5–7].

Since the Colombian Caribbean has agricultural communities, whose working conditions are like the ones found in areas where patients suffer from MeN, it was decided to explore whether this entity could also be found in this area. At the same time, it was decided to evaluate the degree of renal impact of a working day under conditions of physical and climatic demands.

Material and methods

A descriptive, observational, cross-sectional study was carried out, based on field work in a farm placed in an area with very hot weather (average 40°C), at 5 meters above sea level, in Sitio Nuevo (Magdalena, Colombia) and with a sample of 28 rural worker volunteers (rice fields).

Study participants consumed water *ad livitum* from study-instituted bottles. The amount consumed was measured and documented by study staff. The workers were evaluated twice during their working hours: 1) at approximately 6:00 AM before starting their work in the morning and 2) at approximately 5:00 PM at the end of the workday. The urine and blood

samples were obtained in the field, and the latter were locally centrifuged. All the samples were stored in refrigerated containers (4°C) and soon transported to the central laboratory of Clínica de la Costa, in Barranquilla city (located 30 minutes away). The parameters measured were their weight, blood pressure, blood samples to measure hemogram, creatinine, urea, glucose, albumin, sodium, chloride, potassium, calcium, phosphorus, magnesium, uric acid and osmolarity, and spot urine sample to measure urine protein, and osmolarity. The clinical and biochemical data obtained for each individual was compared to see whether there was a significant difference between its morning and evening values. In those workers who developed acute kidney injury during the workday, defined as an increase of serum creatinine >0.3 mg/dl between its morning creatinine and evening creatinine value, it was also compared for each obtained parameter if there was a significant difference between its morning and evening values.

The statistical analysis was performed applying Wilcoxon signed-rank test. This study was approved by Ethical Committee of Clínica de la Costa, Barranquilla (Colombia), and informed consent was obtained from all patients.

Results

Of the 28 young (x,SD: 25±5 years old) men workers (rice harvesters) evaluated, 5 (18 %) presented a significant increase (>0.3 mg/dl) in serum creatinine during the workday (morning serum creatinine: 0.8±0.15 vs. evening serum creatinine: 1.2±0.17, $p<0.001$). The volume of water ingested by the workers was highly variable (2,861 ± 1,591 cc). There was no significant difference in the amount of hydration between the patients who experienced an AKI (change of $\geq$ 0.3 mg/dl in serum creatinine) during the workday and those who did not suffer it.

Regarding the demographic characteristics of the evaluated individuals, they were of low socioeconomic status, working in agriculture since they were 18 years old, with no known medical comorbidities. They were exposed to agrochemicals and had eight hours workdays with programmed rest periods.

In all the studied volunteers, it was compared for each obtained parameter if there was a significant difference between its morning and evening values. In this sense, statistically significant changes between morning and evening values were found only in six parameters: a significant increase in patients' evening values of serum sodium, glucose, phosphorus, creatinine (they did not reach AKI criteria), urinary osmolarity, as well as a significant reduction in their serum potassium levels, compared to their morning values (Table 1).

Table 1. Modified parameters between morning and afternoon samples in all the studied workers (n = 28)

Parameters	Morning Values mean, standard deviation	Afternoon Values mean, standard deviation	P
Serum sodium (mmol/L)	139.8±1.6	141.1±1.5	<0.001
Serum creatinine (mg/dl)	0.8±0.15	0.99±0.17	<0.001
Serum potassium (mg/dl)	4.6±0.4	4.2±0.4	<0.001
Serum phosphorus (mg/dl)	3.4±0.5	3.9±0.5	<0.001
Serum uric acid (mg/dl)	5±1	4±1	0.04
Serum glucose (mg/dl)	87.4±13	95.9±21	0.03
Urinary osmolarity (mOsm/L)	653±208	745±207	0.015
Serum urea (mg/dl)	27±4	32±8	0.9
Serum chloride (mg/dl)	104±2.8	105±2.3	0.09
Serum calcium (mg/dl)	9.5±0.3	9.6±0.3	0.2
Serum magnesium (mg/dl)	2±0.1	2±0.1	0.6
Serum albumin (g/L)	4.6±0.3	4.7±0.3	0.3
Urine protein g/dl	0.10±0.1	21±0.7	0.09
Hematogrit (%)	42±3	45±	0.07
Hemoglobin (g/dl)	13±1	14±1	0.08
Leukocytes (mm3)	7330±2000	7400±1800	0.6
Weight (Kg)	66±11	65.5±11	0.2
Systolic BP (mmHg)	123±15	125±17	0.4
Diastolic BP (mmHg)	82±11	79±7	0.4

Note: BP: blood pressure.

Source: Own elaboration.

In those workers who developed AKI during the workday, it was compared for each obtained parameter if there was a significant difference between its morning and evening values. In this sense, statistically significant changes between morning and evening values were found only in 4 parameters: a significant increase in patients' afternoon values of serum creatinine (they reached AKI criteria), sodium, and urinary osmolarity levels, as well as a significant reduction in their uric acid levels, compared to their morning values.

Discussion

Other studies performed in rural workers under similar working and weather conditions have reported similar findings. Kupferman et al. carried out a study based on 326 workers

in Nicaragua during the harvest season, and they found that 10.4 % (n = 34) of the workers developed AKI during harvest, of which 85 % were sugarcane cutters. In addition, multiple linear regression models for serum creatinine showed that working as a cane cutter during harvest was associated with a 16 % increase in serum creatinine value [8].

Peraza et al. conducted a study (n = 664 participants) in El Salvador, between the third and seventh decade of life, in various sort of agricultural jobs and at different altitudes above sea level: 0-50 m, 500-650 m, and 1,650 m, demonstrating that in the communities who were located lower in respect to sea level, 19 % of workers showed a decrease in GFR <60 ml / min per 1.73 m^2. However, this condition was not observed in workers who were more than 500 m above sea level [9]. Although MeN is currently recognized as an independent entity, for many authors it seems to be a variety of a chronic nephropathy reported in different parts of the world, with a common denominator which consists of its apparition in agricultural workers exposed to extreme muscular effort, poor hydration status and very hot climates in low areas [8–12].

In this sense, there is controversy regarding which of the aforementioned inducing factors (extremely hot weather, dehydration status, etc.) could mainly contribute to the appearance of this entity. Regarding excessive physical exertion, recent studies have put in doubt its benefits since they documented a "J curve" in its association with general mortality. Respecting the possible relationship between a hard physical activity with the appearance of acute kidney injury, various mechanisms have been postulated [13–15]: First, extreme exercise promotes renal hypoperfusion, and consequently leads to glomerular filtration rate reduction. This phenomenon can be exacerbated by volume depletion due to excessive fluid loss and its inadequate replacement, as well as an extreme intra-renal vasoconstriction as a result of a marked sympathetic system activation (increased catecholamines), and renal vasoconstrictor hormones release, as is the case of vasopressin, and renin-angiotensin-aldosterone system. It should be noted that intrarenal vasospasm as a mechanism of AKI has already been documented in the ALPE syndrome: exercise-induced AKI developing after anaerobic exercises [13–15].

Second, renal damage induced by substances which are high in serum compartment, mainly as a consequence of rhabdomyolysis, such as phosphorus, uric acid (crystal nephropathy) and myoglobin (pigment nephropathy) can induce renal damage. These substances can precipitate within the proximal tubules, causing obstruction and exacerbating their toxic impact. The tendency for intra-tubular precipitation is intensified by the elevated concentration and acidity of urine in this environment [13, 14]. There are different mechanisms through which uric acid can cause kidney injury, such as: renal autoregulation alteration, intra-renal

vasoconstriction, endothelial dysfunction, as well as uric acid pro-inflammatory (increased IL-6) and pro-oxidative effects [15–20]. Third, regarding the hypothesis that recurrent heat stress (heat stroke) could lead to renal damage, it has been postulated that it could act by promoting critical fluid contraction, muscle thermal damage, as well as vasoconstrictor substances release [13, 21]. In addition, it has been proposed that repetitive dehydration leads to tubular damage and parenchymal fibrosis since during dehydration aldose reductase and fructokinase enzymes are activated in renal tubules, inducing higher intratubular fructose synthesis, higher fructose metabolism, and consequently increased oxidative tubule-interstitial damage [18]. Moreover, this clinical scenario usually is worsened by the workers' cultural customs of drinking fructose-containing drinks [9, 13]. However, some authors do not consider this mechanism as the main inducing factor of CINAC. They base their statement in a series of facts which are summarized in the PRO column of Table 2 [5].

Fourth, other authors attribute a prominent role to nephrotoxicity induced by NSAIDs, heavy metals, and/or agrochemicals (fertilizers and pesticides) [9–13]. Pesticides contain nephrotoxic agents such as cadmium, arsenic, chromium, and other heavy metals. Chronic exposure to those substances has been associated with chronic tubulointerstitial nephritis. The damaging mechanism consists of the accumulation of these metals in proximal tubule cells, where they cause functional and structural defects. This process involves local oxidative stress, which leads to lipid peroxidation, apoptosis and necrosis of renal cells [22].

Fifth, a possible genetic susceptibility to develop this condition has also been proposed, since it has been documented an association of CINAC with family history of CKD, as well as a relationship between CINAC and single nucleotide polymorphisms in the SLC13A3 and KCNA10 genes in rural workers in Sri Lanka [9].

Therefore, all the above described AKI inducing mechanisms, such as extreme exercise, pigmenturia, heat stroke, nephrotoxic agents, and genetic predisposing factors could induce, individually or combined, repetitive AKI episodes in rural workers, and consequently lead them to develop CKD [23, 24].

In our study some volunteers presented a significant change between morning and afternoon values of the following parameters: Serum sodium, glucose, phosphorus, creatinine, urinary osmolarity levels, as well as a significant reduction in their serum potassium levels. Regarding the documented significantly higher serum sodium, serum creatinine and urinary osmolarity afternoon values compared to their morning values, they could reflect the marked status of dehydration of these workers. Besides, the documented significantly higher serum

Table 2. Arguments in favor (PRO) or against (CON) dehydration as the main inducing factor of chronic interstitial nephritis in agricultural communities (CINAC)

CON	PRO
CINAC has not been documented among rural workers in the majority of tropical areas of the world.	The severity of dehydration depends not only on the environmental heat but also on the individual's adequate hydration and his/her renal water reabsorption capacity.
CINAC has been documented in individuals who live in agricultural communities, but they are not rural workers.	Although these individuals are not rural workers, they are exposed to the same climate of extreme heat, and therefore to repeatedly suffer dehydration and its potential renal consequences.
Chronic kidney disease has not been reported among workers exposed to hot environments during their work (eg: iron foundries, glass factories, etc.) in non-agricultural communities.	Dehydration could be not the main cause but a cofactor of some other kidney-damaging agent, such as agrochemicals.
Factitious serum creatinine elevation at the end of the workday, could be explained by hemoconcentration, low-grade muscle injury, etc. This could be a confounding factor, particularly since KDIGO criteria requires just a small creatinine elevation (0.3 mg/dl) to diagnose acute kidney injury.	This point could be clarified by performing further evaluations, such as re-evaluating creatininemia after re-hydration (solving hemoconcentration) and accompanying serum creatinine dosage with that of serum cystatin C (not influenced by muscle injury).
There is not enough scientific evidence yet in favor that repeated dehydration could be the main inducing cause of CINAC.	
Animal models that documented acute kidney injury with subsequent development of fibrosis in relation to the activation of fructokinase, were subjected to much more heat and dehydration compared to rural workers.	The heat dose required by these animals to develop kidney damage could be much higher than that required by a human being.

Source: Own elaboration.

glucose afternoon values compared to their morning values, could reflect that perhaps some volunteers suffered from pre-diabetes mellitus, and/or the high stress status stand (high sympathetic tone) by these workers. Concerning the documented significantly higher serum phosphorus (and serum creatinine) values compared to their morning ones, they could be explained by some degree of rhabdomyolysis induced by their harsh physical effort. Finally, the documented significantly reduced serum potassium values compared to their

morning values, could be explained by and increased urinary potassium loss secondary to secondary hyperaldosteronism (induced by hypovolemia), and/or some degree of proximal tubule dysfunction (acquired or primary tubulopathy). An acute proximal tubular injury with its consequent urine uric acid loss could also explain the serum uric acid level reduction documented in the afternoon samples in our study.

In regard to the documented significantly higher serum creatinine, as well as serum sodium and urinary osmolarity afternoon values compared to their morning values, they could reflect on one hand AKI installation, and on the other hand, a status of marked dehydration, being probably their main AKI inducing mechanism. Finally, the documented significantly reduced afternoon serum uric acid values compared to their morning ones, could be explained by some degree of proximal tubule dysfunction (acquired or primary tubulopathy) and increased urinary uric acid loss or intratubular precipitation. Uric acid intratubular precipitation could be promoted by dehydration [16–20]. As it was mentioned above, intratubular uric acid accumulation can induce tubular damage by promoting local ischemia, inflammation, and oxidative stress [15, 20, 25].

Studies performed in Brazil, El Salvador and Nicaragua also found an increase in serum creatinine after a heavy workday, documenting a mean serum creatinine increase of 0.21 mg/dl, 0.12 mg/dl, and 0.12 mg/dl, respectively [22–31]. Even, in the Brazilian study, 17 % of the studied workers (5/28) showed a serum creatinine rise $\geq$ 0.3 mg/dl at the end of the workday [26].

It is worth pointing out that despite the aforementioned in favor and against the role that repeated dehydration could play in the induction of CINAC, and the known worsening effect that it has in other renal conditions such as urolithiasis, and acute or chronic nephropathy of any etiology, it seems that at least severe dehydration has a co-causal role in the appearance of CINAC. Finally, since this nephropathy has also been documented in other sort of workers exposed to hot climate (masons, long haul truckers), as well as in people not-exposed to hot-stress (workers' relatives), we prefer the term environmental-stress nephropathy to designate this entity [21].

The main limitations of our study have been the relative low number of workers studied, not having been able to dose agrochemicals, nor obtain the thermal record in the field by using heat stress monitors on the day the study was carried out, as well as having studied only one agriculture setting. We plan to overcome all these limitations in our next field study.

Conclusion

Eighteen percent of the rural workers evaluated developed parameters compatible with AKI and dehydration at the end of workday in the Colombian Caribbean countryside. It is essential to clarify the role of dehydration in the development of chronic interstitial nephritis of agricultural communities (CINAC), given the simplicity of its prevention and the impact that this would have on the rural workers health.

Authors Contributions

Carlos Musso: conceptualization, research, methodology, writing (original draft), writing (review and editing of manuscript); Gustavo Aroca: data curation, research, methodology, visualization, writing (revising and editing the manuscript), writing (revising and editing the manuscript); Lil Avendaño-Echavez: supervision, writing (original draft); Andrés Cadena-Bonfanti: conceptualization, research; Luis Castillo: conceptualization, research; Henry González-Torres: methodology; Juan C. Conde: data curation; Elkin Navarro-Quiroz: data curation; William Peña-Vargas: data curation; Sandra Hernandez: data curation; Maria de los Ángeles Velez-Verbel: data curator, writing (original draft); Rafael Perez: data curation; Angélica Sierra: data curation; Zenen Rua: data curation; Jorge Palmera: data curation; Sergio Terrasa: methodology.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patients.

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Conflicts of interest

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