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Polar Views in Nephrology

Pro: Heat stress as a potential etiology of Mesoamerican and Sri Lankan nephropathy: a late night consult with Sherlock Holmes

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ABSTRACT

Epidemics of chronic kidney disease are now recognized in Central America, Mexico, India and Sri Lanka, and there is also some evidence that similar epidemics may be occurring in the USA, Thailand and elsewhere. A common denominator for each location is manually working outside in extremely hot environments. Here we review the evidence that the primary etiology may be heat stress related to repeated subclinical or clinical acute kidney injury that eventually manifests as chronic kidney disease. In some aspects, the disease may manifest as subclinical heat stroke, subclinical rhabdomyolysis or a subclinical tumor lysis syndrome. While toxins could be involved, it would be difficult to attribute this as a main mechanism, given the wide range of occupations and geographic regions manifesting this disease. While some of the epidemics may be due to better reporting, we believe the most important reasons are increasing heat extremes (heat waves) coupled with hydration with sugary or, less commonly, alcoholic beverages.

Keywords: CKD, epidemiology, ESRD, fructose, uric acid

In my dream last night, I once again had the opportunity to visit 221B Baker Street to consult with my friends, the honorable Dr John Watson and Mr Sherlock Holmes. Dr Watson met me at the door, wearing his Oxford tweed jacket with bowtie, this time appearing a little bit more portly than before.

'Good to see you, Johnson. Here to talk about sugar again?' Watson said with a smile as he offered a tray of chocolates to me.

'No, Watson, not this time', I said as I quickly took a chocolate. 'But I have been asked to defend an argument, and I could use some advice.'

Watson took me back to the living room den where I found Holmes in his usual chair, reading a book on maritime history as he smoked his pipe. As I entered the room, Holmes looked up and cracked an almost imperceptible smile.

'Holmes, there is an epidemic of chronic kidney disease (CKD) that has emerged since the 1970s in Central America. It tends to affect sugarcane workers living on the Pacific Coast. Similar epidemics are occurring in India and Sri Lanka, and there is some evidence that it is more widespread and affects other areas in Southeast Asia, sub-Saharan Africa, Mexico and certain regions in the USA. So far more than 40 000 people have died [1, 2].'

'It sounds like it could be a toxin. There are so many chemicals used these days, the wells are likely contaminated. Has testing been done?' Watson spoke.

'Yes, that is the hypothesis I am debating against—it certainly is an emotional issue, as the workers are subjected to harsh working conditions and have lots of exposures. Yet to date, no toxin has been identified, and while there are drugs, toxins and infections that may cause CKD, the clinical characteristics do not fully mirror the current epidemics' (Table 1).

'Emotional qualities are antagonistic to clear reasoning [*The Sign of the Four*]', said Holmes sternly to Watson as he blew a smoke ring into the air. 'As a rule, the more bizarre a thing, the less mysterious it proves to be [*The Red-headed League*]. I make a point of never having any prejudices, and of following docilely wherever fact may lead me [*The Reigate Puzzle*]. So always approach a case with an absolutely blank mind. It is always an advantage. Form no theories, just simply observe and draw inferences from your observations [*The Adventure of the Cardboard Box*].'

'Holmes, we do have some observations that have led to the hypothesis that heat stress may be the cause. I realize that it is not necessarily a sexy cause, but the data appear strong', I said quietly.

'Do not bias my mind by suggesting theories or suspicions. I wish you simply to report facts in the fullest possible manner to me, and you can leave me to do the theorizing [*The Hound of*

Table 1. Toxins and infections associated with acute and CKD

Etiology	Past epidemic	Epidemiology	Acute	Chronic	Biopsy	Ref
Lead	Queensland (1920s)	Children (paint)	Neuro (wrist drop, ocular palsies) Abdominal colic Ocular (optic neuritis) Fanconi syndrome	CKD Hypertension Gout Anemia	CIN; Glomerulosclerosis Microvascular lesions	[3]
Cadmium	Toyama (1930–60s)	Contaminated river Rice paddies	Bone pain Glycosuria, proteinuria Hypophosphatemia	Osteomalacia Fanconi, glycosuria	CIN	[4]
Arsenic	Manchester (1900s)	Beer contamination	Abdominal pain Neural and vascular	Hyperkeratoses ?Albuminuria, CKD		[5, 6]
Leptospirosis	Philippines (2009)	Water contamination	Conjunctival suffusion Myalgias and fever Acute interstitial nephritis Jaundice, meningitis (rare)	?CKD		[7, 8]
Hantavirus	Korean War (1953)	Field mouse	Fever, myalgias, petechiae Albuminuria	? CKD	AIN, hemorrhage	[9]
Aristolochia	Balkans (1940–2000), Brussels (1990)	Contaminated wheat Contaminated 'slimming herbs'	Proteinuria, glycosuria Rapidly rising creatinine	CIN, uroepithelial CA; Mild hypertension Anemia	CIN	[10]
Ochratoxin A	?Northern Africa	Contaminated foods Cereal, nuts	Glycosuria, proteinuria	CIN?	CIN (animals)	[11]
Analgesic abuse	Australia, Belgium (1950–80s)	Phenacetin-containing analgesic combinations	AIN, papillary necrosis, sterile pyuria, hematuria Polyuria	CIN, hypertension, uroepithelial CA	CIN	[12]
Organophosphates (anticholinesterases)		Agrochemicals	Salivation, diarrhea Abdominal pain Tachycardia, tremor Seizures, AKI (rare)	?CKD	?	
Paraquat Glyphosate		Herbicide Agrochemical	ARDS, rare AKI, liver Abdominal pain, AKI, liver failure, low BP	?CKD, Parkinson's ?CKD		[13, 14]

Key: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease; CA, cancer, CIN, chronic interstitial nephritis.

the Baskervilles]. Before we start to investigate, let us try to realize what we *do* know, so as to make the most of it and to separate the essential from the accidental [*The Adventure of the Priory School*]. [The best approach is to reason backward from effects to causes [*The Adventure of the Cardboard Box*]'. [So give me] Data! Data! Data!', Holmes cried impatiently. 'I can't make bricks without clay [*The Adventure of the Speckled Band*].'

'So, a common finding is that the disease is occurring in areas of the world that are extremely hot, exposing the workers to temperatures that are considered dangerous for prolonged work. Indeed, heat exposure is always the common denominator, for while the disease is highest in sugarcane workers, in the epidemic in Central America it has also been observed in construction workers, port workers, fisherman and those working in other agricultural occupations (banana, cotton). There is also the finding that sugarcane workers who are working at higher altitudes where the temperature is cooler have a lower frequency of CKD [2].'

'Many subjects also develop symptoms and signs of heat stress or dehydration, which is known to cause renal dysfunction. Indeed, there is some evidence that markers of acute kidney injury can occur during work shifts as well as overwork seasons [15].'

Watson slapped his knees. 'I found a flaw. Dehydration causes a reversible type of renal disease and is not associated with structural injury. Severe heat stress can cause heat stroke in which acute tubular necrosis (ATN) occurs from hypotension or rhabdomyolysis. However, recent studies suggest the renal injury is acutely associated with fever, leukocyturia and acute interstitial nephritis. This cannot be from heat. Surely there is a toxin.'

'Perhaps', I replied. 'But let me argue otherwise by discussing heat stroke, which has been recognized since Roman times [16] and for which there have been many epidemics, including in Chicago in 1995 [17], in Lyon, France in 2003 [18] and in Karachi in 2015 [19]. Heat stroke occurs when the body overheats, and the acute presentation includes fever, confusion and symptoms of dehydration. Subclinical rhabdomyolysis is common, and acute renal failure can result from leukocyturia and hematuria and nonnephrotic proteinuria, with the renal biopsy showing interstitial inflammation and tubular injury. Other features include hypokalemia, hypophosphatemia, elevated serum lactate and hyperuricemia [20, 21]. Subjects with heat stroke

have also been reported to develop CKD over time, with biopsy showing chronic interstitial nephritis with some glomerulosclerosis [21]. These clinical signs and histologic findings are near identical to what has been reported in Mesoamerican and Sri Lankan nephropathy [2].'

'There is also experimental evidence. Recurrent heat stress in animals induces CKD in mice that can be prevented if hydration is provided during the period of heat stress. The mechanism is mediated in part by vasopressin as well as induction of the aldose reductase–fructokinase system in the proximal tubule by hyperosmolarity. The injury involves tubular damage, local inflammation and chronic scarring, and excessive vasopressin can also induce glomerular changes as may complicate Mesoamerican nephropathy' [22].

'Heat stress and heat stroke are also known to be associated with hyperuricemia, acute increases in uricosuria, acidic urine and urate crystal formation [21, 23]. Hyperuricemia is also common in subjects with Mesoamerican nephropathy, as well as from other regions (Sri Lanka and India), and we found urate crystals in 20% of sugarcane workers at the end of the workday [15, 24]. On one of the hottest days of the year in 2013, we found high levels of urine uric acid and urate crystals in all seven subjects studied, which were similar to those observed in tumor lysis syndrome [25]. Thus, uricosuria may also be causing disease, either through crystalline or noncrystalline pathways [26, 27].'

'This is a strong evidence, but then why is the epidemic now? This should be something that was always present,' said Watson with a look of incredulity, as he grabbed another chocolate.

'Well, I believe it actually has been, but that it is increasing now because of better recognition and because of climate change. While it is true that mean temperatures have only increased by 0.8–1.0°C in the last century, there has been a dramatic increase worldwide in heat extremes, which manifest as heat waves [28, 29]. I suspect that the heat stress–associated injury occurs most frequently during the heat waves when subjects are least prepared. In addition, rehydration with soft drinks containing fructose amplifies the injury by causing further urinary concentration and uric acid generation and providing substrate for proximal tubular fructokinase, thus providing a perfect storm [30].'

Holmes looked up at me and stared with his steely eyes. 'And the counterarguments? One should always look for a possible alternative and provide against it. It is the first rule of criminal investigation [*The Adventure of Black Peter*].'

'Of course, there are those who challenge the hypothesis. One of the biggest arguments is that it should be observed in other hot areas. As an example, some have argued that it should be in northern Sri Lanka, yet there are no reports of it there [31].'

'Are there any reports that it is not there, specifically with screening of serum creatinines or some other careful method?'

'No, there are no reports at all.'

'Elementary, Johnson! Absence of evidence does not mean evidence of absence.'

'And indeed, new hot spots are being identified every year, including in Thailand and the USA [2].'

Watson looked up. 'But what about Cuba? I understand they have better surveillance there, and that Mesoamerican nephropathy is not observed there.'

'Well, I do have a hypothesis.'

'Yet another hypothesis, Johnson?' Holmes said as he cast a mischievous look in my direction. 'Bravo. There should be no combination of events for which the wit of man cannot conceive an explanation [*The Valley of Fear*].'

'So the regulation of body temperature is largely governed by mitochondrial metabolism and by the efficiency by which mitochondria generate adenosine triphosphate (ATP). When mitochondria make ATP, they also generate heat, and these occur in opposition, in that the more effectively oxidative phosphorylation is coupled, the more ATP and the less heat that is generated, whereas if oxidative phosphorylation is "less coupled", then more heat is generated with lesser amounts of ATP [32]. In this regard, there is evidence that Native Americans, who historically travelled across Siberia and the Bering Strait into America, acquired mutations that led to increased mitochondrial uncoupling, leading to greater heat generation during metabolism that likely provided a survival advantage in cold environments compared with Africans whose mitochondria are tightly coupled [33, 34]. While this would have provided a survival advantage in cold environments, in hot environments it would be expected to increase the risk for heat stress and heat stroke. Thus it could explain why Hispanics living in Central America, who have a high admixture of Native American genes, might be at increased risk for developing heat stress nephropathy while Hispanics living in Cuba, who have a higher African admixture of genes, might be relatively protected [32–35].'

'This sounds testable', smiled Watson.

'Yes, one balances probabilities and chooses the most likely. It is the scientific use of the imagination [*The Hound of the Baskervilles*]', Holmes said, as the smoke billowed over his head. 'Johnson, are there any bits of evidence that confuse you?'

'Well, yes, there are. For example, in Sri Lanka there is some evidence that areas with shallow wells have higher rates of CKD. Since shallow wells might accumulate more toxins, this argument could support the toxin argument. On the other hand, the locals there are concerned that chemicals may be in the well water, so this could lead to less water intake and greater risk for dehydration. Indeed, in the same study the intake of less water (<3 L/day), greater sun exposure and longer (>6 h/day) working hours was associated with increased risk for CKD [36]. If well water is the cause of the CKD, then lower intake would not be expected to be a risk factor.

In contrast, while most studies suggest that subjects developing Mesoamerican nephropathy tend to show evidence for dehydration [15, 37], there are two cross-sectional studies that report higher water intake in subjects with CKD [38, 39]. These data would also be consistent with a toxin in the drinking water playing a role in the epidemic. Alternatively, it could be that many of the subjects knew they had CKD and, because it is largely believed by the workers that dehydration is playing a role in the disease, they might be drinking more to protect themselves or because CKD from chronic interstitial nephritis can impair urinary concentration in subjects.'

Holmes nodded his head. 'Circumstantial [cross-sectional] evidence is a very tricky thing,' answered Holmes thoughtfully. 'It may seem to point very straight to one thing, but if you shift your own point of view a little, you may find it pointing in an

equally uncompromising manner to something entirely different [*The Boscombe Valley Mystery*].'

Watson stood up. 'Yes, we need longitudinal data to better understand this disease. Are there not some data that low water intake in general is a risk factor for CKD?'

'Yes, not only does low water intake predict CKD, but also a low urine pH and high serum uric acid [40–42]. High serum copeptin, which marks high vasopressin levels, also predicts the development of CKD. There are even studies that suggest bicarbonate intake may slow CKD through unknown mechanisms, which I believe might include urinary alkalinization. Thus, Mesoamerican nephropathy may simply reflect the tip of the iceberg and heat stress and dehydration may be more pervasive risk factors for CKD than we currently appreciate.'

'Very well,' smiled Watson, 'you have a good argument, and most importantly, it is testable.'

Holmes nodded, 'And remember, once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth [*The Sign of the Four*].'

I stood up and thanked both of them and headed to the door, but turned around one last time to see Holmes had resumed reading, still blowing smoke rings in the air.

'You know, Holmes, smoking is not good for your health.'

'Aha, Johnson, you see but you do not observe. The distinction is clear [*A Scandal in Bohemia*]. I may appear to smoke, but I do not inhale. Until next time'.

I bowed my head and headed back home, where I completed a very restful sleep.

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CONFLICT OF INTEREST STATEMENT

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(See related articles by Zoccali. Causal mechanism and component causes in Mesoamerican–Sri Lankan nephropathy: the moderator's view. *Nephrol Dial Transplant* 2017; 32: 607–610; Campese. Con: Mesoamerican nephropathy: is the problem dehydration or rehydration? *Nephrol Dial Transplant* 2017; 32: 603–606)

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Opponent's comments

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Dr Johnson makes a very strong argument that dehydration, heat stroke and hyperuricemia may be responsible for Mesoamerican nephropathy (MeN). To do so, he resurrects Sherlock Holmes and John Watson and asks for their advice.

Dr Johnson at the end takes for granted the conclusions of Mr Holmes, because Mr Holmes cannot be wrong. Unfortunately, the last sentence of Mr Holmes proves that even he can be wrong if not provided with the right information. He concludes: the distinction is clear, 'I may appear to smoke, but I do not inhale'. Dr Johnson had forgotten to tell poor Mr Holmes that nicotine is liposoluble and can be absorbed by the oral mucosa. In other words, Mr Holmes was flatly wrong; indeed, he was smoking.

Dr Johnson also ignores a smart advice by Mr Holmes: 'And remember, once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth'. The key works here are 'once you eliminate the impossible'. Dr Johnson, in his brilliant analysis, forgets to eliminate other possibilities.

I totally agree with Dr Johnson that dehydration, heat stroke and rhabdomyolysis are important elements of MeN. I do not believe they are the main factors, because the available evidence does not support his theory.

In the study by Fischer *et al.* [1], 255 patients were admitted to a hospital in Nicaragua with the diagnosis of AKI related to MeN. In this group of patients, only 30% manifested hyperuricemia, only 12% manifested elevated levels of creatinine phosphokinase and most patients presented with hypokalemia. All these features are not compatible with the diagnosis of heat stroke or rhabdomyolysis. Moreover, 30 years ago there was no evidence of the disease, although the working hours and working conditions were much worse than at present.