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Editorial Comment

EDITORIAL COMMENT

Solving the riddle of Aguascalientes nephropathy: nephron number, environmental toxins and family clustering

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ABSTRACT

Aguascalientes, Mexico, has a high incidence and prevalence of advanced chronic kidney disease (CKD). CKD is especially frequent in young people ages 20–40 years in whom the cause of CKD was unknown, although kidney biopsies frequently showed focal segmental glomerulosclerosis (FSGS) and glomerulomegaly. Macias-Diaz *et al*. have now pursued this lead by screening teenagers in Calvillo, one of the hardest hit municipalities. They uncovered clinical, laboratory, kidney biopsy and exposure findings that define a new entity, Aguascalientes nephropathy, and are consistent with familial exposure to common environmental toxins, potentially consisting of pesticides. They hypothesize that prenatal exposure to these toxins may decrease nephron number. The young age of persons with FSGS would be consistent with a novel environmental toxin introduced more than 50 years ago but not present in the environment before. Key takeaways from this research are the need to screen teenagers for albuminuria, to provide kidney-protective strategies to patients identified as having CKD and for the research community to support Aguascalientes nephrologists and health authorities to unravel the cause and potential solutions for this CKD hotspot. In this regard, the screening approach and the cohort generated by Macias-Diaz *et al*. represent a giant step forward. The next steps should be to screen younger children for albuminuria and kidney size and to identify the putative toxins.

Keywords: burden of disease, CKD of uncertain etiology, CKD hotspot, familial, focal segmental glomerulosclerosis, Mexico, pesticides

THE AGUASCALIENTES CKD HOTSPOT

Chronic kidney disease (CKD) hotspots are countries, regions, communities or ethnicities with a higher-than-average incidence of CKD [1]. Parts of Central America are CKD hotspots and the site of Mesoamerican nephropathy [2–4]. Mesoamerican nephropathy is associated with male gender, agricultural work, water intake and lowland altitude, likely reflecting the impact of higher temperature and humidity. There is frequently a family history of CKD, potentially implying a genetic background, common intrafamilial exposure or a combination of both [5, 6]. However, there are no significant associations with pesticide exposure, non-steroidal anti-inflammatory drugs, heat stress or alcohol consumption. More recently, Aguascalientes

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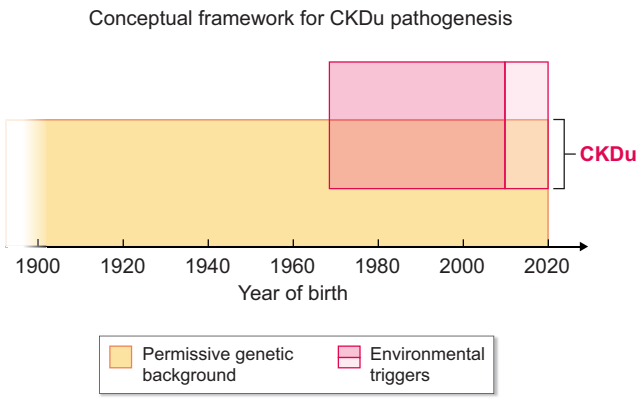

FIGURE 1: Conceptual framework for CKDu: the Aguascalientes hotspot as an example. Based on available evidence regarding the concentration of CKD cases within certain geographic locations and families, as well as on the association with certain environments and occupations, a conceptual framework implying a genetic susceptibility background in association/interacting with environmental exposures is a reasonable starting point to unravel the pathogenesis of CKDu. However, the familial incidence may also be due to familial exposure to the same environmental actor and/or to a shared microbiota pattern. The genetic background may be expected to have been present for centuries unless significant immigration occurred in recent decades. The age pattern evidenced by KRT and kidney biopsy epidemiology points to the initiation of the CKD hotspot in Aguascalientes ~50 years ago, which may be hypothesized to be the date of the introduction of an environmental factor, and the more recent data on albuminuria and decreased kidney size in teenagers suggest that the CKD hotspot was still active 10–15 years ago and potentially today.

has emerged as one of the hottest CKD hotspots in Mexico and is among the hottest in the world for 20- to 40-year-olds [7]. A well-coordinated research effort led by José Manuel Arreola Guerra is collecting the kidney replacement therapy (KRT) incidence and prevalence in a KRT registry published with the US Renal Data System report and also the causes of CKD with histological confirmation in a kidney biopsy registry [7, 8]. The combination of KRT and kidney biopsy registries identified an atypical age pattern characterized by an average age of 46 years at KRT initiation in Aguascalientes, with peaks at ages 20–40 and 50–70 years. CKD of unknown origin (CKDu) was the main cause of KRT (73% of KRT cases) in Aguascalientes, especially for those ages 20–40 years, followed by diabetes, in contrast to Kidney Early Evaluation Program data for Mexico City and Jalisco, in which diabetes was the main cause of CKD [9]. Moreover, kidney biopsy showed a high prevalence of focal segmental glomerulosclerosis (FSGS) of unknown origin with glomerulomegaly in young Aguascalientes patients, which differed from the predominantly tubulointerstitial injury of Mesoamerican nephropathy or Sri Lankan CKD of unknown origin [9].

Both genetic and environmental factors may contribute to the Aguascalientes CKD hotspot [9]. The Aguascalientes CKD hotspot was recently identified and patients are young, pointing to recently introduced environmental factors or to the interaction of new environmental toxins with a permissive genetic background as drivers of the disease (Figure 1). Determining the precise timing of the emergence of the regional CKD hotspot is essential to identify coetaneous environmental factors that may enable or cause CKD. In this regard, the 20–40 years age range peak is consistent with an environmental factor introduced within the last 50 years. However, describing environmental timelines is not an easy task, as environmental changes may increase the intensity of exposure over time until a critical exposure threshold causes harm. Moreover, the population may not be universally sensitive to the same thresholds. Additionally, environmental exposures may impact adults, children and even newborns through their mothers during pregnancy, potentially to different degrees. Finally, for chronic diseases such as CKD, there may be a lag time that may last for decades before becoming clinically evident or needing KRT, as is the case for genetic kidney diseases such as Fabry disease or autosomal dominant polycystic kidney disease [10, 11]. It is even possible that by the time the CKD hotspot has been identified, the environmental factor is no longer active or present.

AN AGRICULTURAL COMMUNITY AND FSGS AS GUIDING CLUES FOR THE CHARACTERIZATION OF A NEW FORM OF CKD

The Aguascalientes municipality with the highest prevalence of KRT is Calvillo, the largest guava producer in Mexico. This raises the issue of the potential contribution of an agricultural link (e.g. through pesticide use) in the pathophysiology of the syndrome, either through ground or water contamination or unsafe direct exposure [12]. Malathion [13, 14] and cypermethrin [15, 16] have been associated with impaired kidney function and nephrotic syndrome [14]. Additionally, fluoride levels above the Mexican standard have been observed in Calvillo water [7]. Exposure to fluoride can cause kidney injury and FSGS [17] and maternal exposure may lead to kidney disease in offspring during puberty [18].

Although the most frequent kidney biopsy pattern in Aguascalientes was FSGS, nephrotic syndrome was uncommon, suggesting a secondary form of FSGS such as hyperfiltration-mediated podocytopathies. These are characterized by the coexistence of FSGS and glomerulomegaly in kidney biopsies, a feature found in 62% of biopsies of young patients in Aguascalientes [7]. Glomerular hyperfiltration is an adaptive response to congenital or acquired low nephron number. When acquired later in life, the causal kidney injury may lead to scarring, i.e. kidney fibrosis. Low nephron endowment at birth causes a reduced kidney mass and hyperfiltration-mediated podocytopathy and may be due to genetic causes or pregnancy-related factors [19].

FURTHER DEFINING THE TIMELINES AND DEFINING CHARACTERISTICS OF AGUASCALIENTES NEPHROPATHY

Macias-Diaz *et al.* [20] have set up a cohort of 513 students (mean age 13 years) from Calvillo in whom urinary albumin:creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) were assessed. Nearly 4% had high UACR (>30 mg/g, median 50 mg/g) at baseline, i.e. evidence of CKD category G1–G3/A2–A3, as the mean eGFR in albuminuric students was 112 mL/min/1.73 m^2 and one participant had a GFR <60 mL/min/1.73 m^2 and a UACR >1500 mg/g. Both sexes were affected equally. Despite preserved GFR, patients with pathological albuminuria had a lower kidney volume on ultrasound consistent with CKD. Eighteen underwent kidney biopsy. All biopsies showed partial foot process effacement and 72% had glomerulomegaly. Interstitial fibrosis was mostly absent. Overall, the imaging, histological and analytical findings were interpreted as consistent with congenital low nephron number. Macias-Diaz *et al.* [20] further identified risk facts for pathological albuminuria that included homestead proximity to maize crops, the use of pesticides at the father's workplace, a family history of CKD and blood pressure abnormalities.

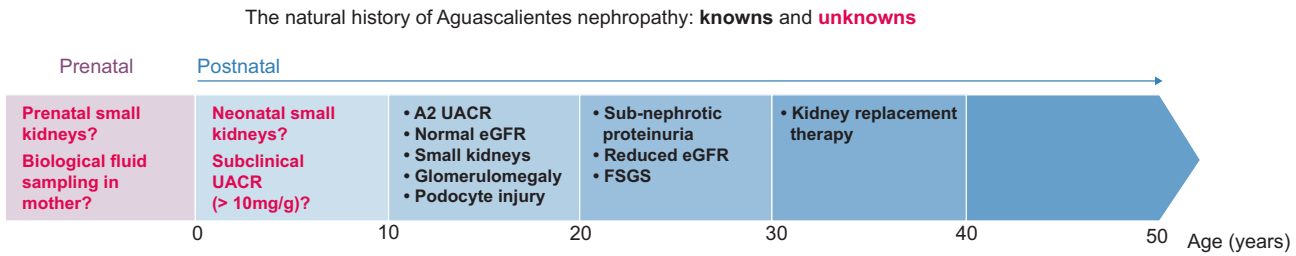

FIGURE 2: The natural history of Aguascalientes nephropathy. Aguascalientes nephropathy is characterized by the presence of pathological albuminuria, decreased kidney size as observed by sonography and preserved kidney function in the second decade of life, associated with histological evidence of decreased nephron number and hyperfiltration-induced podocytopathy in the absence of significant fibrosis, which argues against recent nephron loss induced by acquired kidney injury. This evolves toward proteinuric FSGS in the third decade of life, associated with decreasing GFR that will need KRT peaking at age 30–40 years. It is yet unknown whether the decreased kidney size can be observed in foetuses, neonatally or during the first decade of life, whether this can be used for screening for the condition and when albuminuria first develops. It is also unknown whether conventional antiproteinuric therapy with renin–angiotensin system blockers slows CKD progression, although it does decrease albuminuria. Further unknowns relate to the triggers for the condition, as low birthweight or prematurity do not appear to be responsible, but family clustering and evidence suggesting exposure to agrochemical toxins were uncovered. Another unknown is whether low nephron number was determined in the past and accounts for the condition as a non-modifiable factor or whether continued exposure to a putative environmental toxin is still accelerating the loss of kidney function.

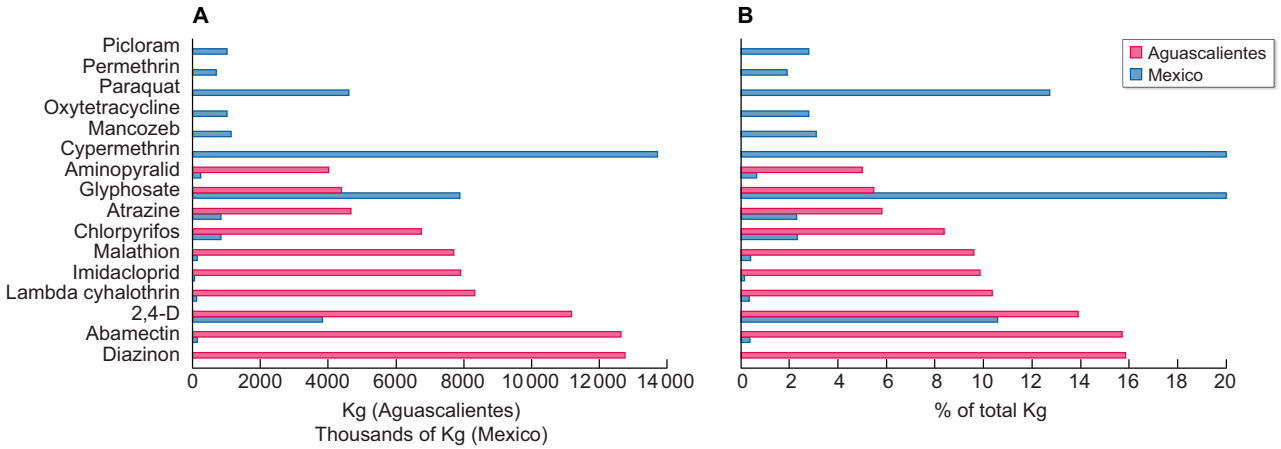

FIGURE 3: Pesticide sales in Mexico and in Aguascalientes. (**A**) Total kilograms. Please note that data for Mexico are expressed as thousands of kilograms and data for Aguascalientes as kilograms. (**B**) Percentage of total kilograms represented by each pesticide. *Source*: Supplementary data, Table S4 from Macias-Diaz *et al.* [20], which used data from the Agrochemicals Marketing Survey 2020, Department of Sanitary Regulation, Aguascalientes, Mexico.

However, Macias-Diaz *et al.* [20] detailed evaluation did not find an association of persistent albuminuria with either birthweight or prematurity, arguing against these factors as drivers of low nephron number. The body mass index and breastfeeding were identified as protective factors.

In summary, Macias-Diaz *et al.* [20] have provided evidence for potential exposure to pesticides (proximity to crops, father's link to pesticides) as a driver of the Aguascalientes CKD hotspot. Together with the characteristic natural history, imaging, histological and analytical features, Macias-Diaz *et al.* have generated enough evidence to define a new entity that, in the absence of firm causal insight, may be termed Aguascalientes nephropathy to differentiate it from other forms of CKD of unknown origin (Figure 2). Nevertheless, some parallelism with Mesoamerican nephropathy is apparent, since both are found in agricultural communities, despite the different climate conditions and biomarker and histological findings [5, 6]. Additionally, both Mesoamerican and Aguascalientes nephropathies are associated with a family history of CKD [5, 6]. Further studies are needed to differentiate a permissive genetic background (which may be responsive only to certain environmental triggers) from common intrafamilial exposure, which is supported by the proximity to crops and father's link to pesticides. A further difference is that Mesoamerican nephropathy is associated with male gender, while Macias-Diaz *et al.* observed similar frequencies of pathological albuminuria in boys and girls [5, 6]. As KRT and kidney biopsies in routine clinical practice in the key young decades of life were more common in men in Aguascalientes, an impact of gender on CKD progression or on later and more persistent exposure to environmental toxins cannot be excluded [7].

Confirming the hypothesis for pesticides as the potential cause of Aguascalientes nephropathy is challenging. Macias-Diaz *et al.* [20] have collected data on pesticide use in the country and in Aguascalientes. If the hypothesis is proposed that this may be a local Aguascalientes issue (which may not be correct), then pesticides overused in Aguascalientes may be of interest for further research. Macias-Diaz *et al.* [20] found clear differences in the types and amounts of pesticides used in Aguascalientes versus Mexico as a whole (Figure 3). Diazinon, abamectin, lambda-cyhalothrin, imidacloprid, malathion, chlorpyrifos, atrazine and aminopyralid appear to be more common in Aguascalientes than in the whole of Mexico. To establish a

causal relationship between these pesticides and nephropathy, the following steps would be helpful: a timeline of the introduction of different pesticides in relationship with the timeline of the Aguascalientes CKD hotspot, identification of any mass intoxication episode and the search for other communities in Mexico or abroad where these pesticides are used or overrepresented and where epidemiological studies similar to the one reported by Macias-Diaz *et al*. [20] can be performed. Additionally, mechanistic studies should assess individual pesticides alone or in combination with other pesticides and fluoride. Evidence for reduced kidney mass at an early age in the absence of fibrosis points to prenatal exposure to toxins causing suboptimal nephrogenesis. Given the age of the subjects, this prenatal exposure was ongoing as recently as 10–15 years ago. Thus it would be prudent to hope for the best but prepare for the worst and assume that the environmental issue is ongoing.

A further interesting epidemiological finding was the decreased risk of CKD in teenagers associated with breastfeeding. This may be used as an argument against prenatal exposure, as breastfeeding may potentially continue to expose the infant to the same environmental factors that the mother was exposed to, if these factors are secreted in maternal milk. An alternative hypothesis explaining the breastfeeding observation relates to the gut microbiota. The impact of the gut microbiota on human health is beyond the scope of this discussion and breastfeeding may impact the gut microbiota [21]. Additionally, diet, drugs and, potentially, environmental toxins interact with the gut microbiota [22–25]. Thus these factors can not only modify the microbiota, but the microbiota may also metabolize and transform dietary components and drugs. The gut microbiota can turn dietary components (e.g. tryptophan) into toxins (e.g. indole) and can also metabolize drugs, potentially increasing or decreasing drug exposure or generating toxic metabolites [23, 26, 27]. Indeed, the microbiota can prevent the toxicity of environmental toxins such as those ingested with diet [28]. An interaction between pesticides, microbiota and the kidney may be the underlying connection to the familial aggregation of CKD cases, as household contacts that share a similar diet tend to share the gut microbiota. The microbiota is also a source of metabolites that may decrease inflammation and protect from kidney injury, including short chain fatty acids such as butyrate and crotonate [29–31].

Finally, antiproteinuric therapy with renin–angiotensin system blockade was initiated in patients with pathological albuminuria. In preliminary results, this was associated with a roughly 40% decrease in albuminuria [20]. Longer-term results in a larger cohort are expected.

AVENUES FOR FURTHER RESEARCH ON AGUASCALIENTES NEPHROPATHY

Key takeaways from the recent manuscript by Macias-Diaz *et al*. [20] are the need for albuminuria screening in Aguascalientes teenagers, the potential utility of kidney protective strategies in patients thus identified and the need for the research community to support Aguascalientes nephrologists and health authorities to unravel the cause and potential solutions of Aguascalientes nephropathy (Table 1). In this regard, the screening approach and the study cohort generated by Macias-Diaz *et al*. [20] represent a giant step forward. Research support is needed to follow and expand the present cohort in number and in scope. Thus the research effort may benefit from screening for albuminuria and sonography in a wider age range of participants, to include younger children and even neonates or adding prenatal sonography to the screening tools. After answering the research question of whether sonography identifies earlier stages of the disease characterized already by small kidney size that precedes the increase in albuminuria, prenatal or neonatal sonography may eventually be used to identify mothers who may have been exposed to nephrotoxins and to collect biological samples that may contain the toxin(s). If indeed a decreased kidney size precedes albuminuria, sonography may become the basic screening tool that informs on exposure prenatally or postnatally and eventually helps to assess the activity status of the CKD hotspot. The epidemiological study should be expanded to affected and unaffected family members to map current and past exposure to different pesticides as well as heavy metals. Additionally, funding should support a biobank of biological samples ranging from blood and urine to feces for microbiota assessments and kidney biopsy tissue remaining after a diagnosis has been achieved. These samples may be used for the identification of specific toxins or metals or their molecular fingerprints as well as for systems biology studies that provide insights into pathogenesis or biomarkers. In family units, genetic testing to identify gene variants that segregate with CKD may be informative. Finally, preclinical studies should address the impact of the identified environmental toxins, alone and in combination, on kidney cells at diverse stages of development.

Table 1. New and persistent research questions on Aguascalientes nephropathy

Is there an environmental factor?
What would this/these factor(s) be?
When did the Aguascalientes hotspot develop?
Is the environmental factor still active and in need of solution?
Is Aguascalientes nephropathy limited to Aguascalientes or are there other examples worldwide?
What are the cellular and molecular mechanisms of injury?
Is kidney injury already present in neonates or foetuses?
If not, when does it become evident?
What is the best screening tool for the early detection of Aguascalientes nephropathy?
What is the natural history and can it be modified by therapy?
What would be the optimal therapy among the different nephroprotective strategies available (conventional RAS blockade, SGLT2 inhibitors, MRA)?

RAS: renin–angiotensin system; SGLT2: sodium–glucose cotransporter protein 2; MRA: mineralocorticoid receptor antagonist.

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CONFLICT OF INTEREST STATEMENT

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