Hypertensive Nephrosclerosis: Diagnosis or Myth

Crystal A. Gadegbeku, MD, FAHA, FACP
Section Chief, Nephrology, Hypertension and Kidney Transplantation

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Hypertension: 2\textsuperscript{nd} Most Common Cause of ESRD

Incident ESRD
Adj: age/gender/race.

Prevalent ESRD
Adj: age/gender/race.
Hypertension Linked to ESRD

Feb. 15, 1873.

THE BRITISH ME.

LECTURES
ON THE
PATHOLOGY, DIAGNOSIS, AND TREATMENT OF BRIGHT'S DISEASE.

By GEORGE JOHNSON, M.D., F.R.S.,
Physician to King's College Hospital; Professor of Medicine in King's College, London; etc.

LECTURE III.—Chronic Bright's Disease.

Small Red Granular Kidney.—Synonyms.—Outward Appearance of the Kidney in different Stages.—General History of the Disease.—Chemical and Microscopical Characters of the Urine.—Microscopic Appearances in the Kidney.—The Structural Changes are essentially tubular and intratubular.—Changes in the Blood-vessels of the Kidney.—Physiological Explanation of the Structural Changes in the Kidney and of the Condition of the Urine.
End-Organ Damage from Malignant Hypertension

**Dysmorphic red cells** Phase contrast microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows). Courtesy of Hans Köhler, MD.
Kidney Injury from Severe Hypertension

- Hyperplastic Arteriolitis
- Fibrinoid Necrosis
Kidney’s Role in BP Regulation

- Pressure Natriuresis
  - Regulation of salt and water
  - Vasopressin, Natriuretic Peptides
- Renin-Angiotensin-Aldosterone System
- Renal Sympathetic Nervous System
- Regulation of Vasoactive Hormones
  - Endothelins
  - Prostaglandins
- Nephron Mass

"the kidney is involved in the genesis of any type of hypertension” A Guyton
What about Hypertension?

- Essential or primary hypertension is a diagnosis of exclusion

- Kidney disease is the most common secondary cause of hypertension

- Hypertension is present in 80% with chronic kidney disease
Hypertension Linked to ESRD

Klag MJ et al, JAMA 277:1293-1298

332,544 Men screened for MRFIT
ESRD Risk by Hypertension Stage

Tozawa M et al. Hypertension 2003;41:1341-1345
THE OLD CHICKEN AND EGG PROBLEM ...

SMACK

WHUMP

1

2
Longitudinal Data on Incident Renal Disease from Hypertension

Natural History of Hypertension (DBP ≥ 90) in 500 patients

- 150 followed PRIOR to development of hypertension
- 350 followed after the development of hypertension

GA Perera, Journal of Chronic Disease, Columbia University, 1955

Fig. 1. Age at onset and age at death of the same 150 patients with hypertensive vascular disease.
Natural History of Untreated Hypertension

- **Hypertensive Complications**
  - 74% develop cardiac hypertrophy by CXR
  - 67% develop “ECG-damage”
  - 50% CHF
  - 12% CVA
  - 14% Retinal hemorrhages
  - 42% Proteinuria
  - 18% Nitrogen retention

- **Death**
  - 43% Sudden Death
  - 22 – 38% Death related to CHF
  - 6 - 10% Death related to Uremia

Perera, GA, J Chronic Dis, 1955;1:33 - 42
Effect of Treated Hypertension on Incident CKD

- Major cardiovascular RCTs demonstrate clear benefit for stroke, MI, and heart failure
- Met-analysis with 26,000 patients
- No impact on kidney function

_Hsu CY J Hum Hypertens 15:99, 2001_
Hypertensive Nephrosclerosis is...?

- Majority of patients with this diagnosis do not have kidney biopsies
- Presumptive diagnosis may be a mixed bag
  - Macrovascular disease
  - Atheroembolic Disease
  - Malignant nephrosclerosis
  - Primary renal disease
  - “Benign Nephrosclerosis”
“Benign” Hypertensive Nephrosclerosis

Hyaline Arteriosclerosis

Fibroelastic Hyperplasia
“Benign” Hypertensive Nephrosclerosis

Glomerular Collapse and Fibrosis
Hypertensive Nephrosclerosis: Diagnostic Inaccuracy

- Term is over-utilized
- Mis-classification bias in African Americans
- Schlessenger Criteria
  - Family Hx, LVH, urine protein < 500 g/day, HT precedes kidney dis.
- AASK Criteria
  - Urine protein to creatinine ratio < 2.0, no other evidence of renal disease (African Americans)
  - Biopsy-confirmed hypertensive nephrosclerosis in 37 of 39 patient
Diagnostic Inaccuracy

- 3100 ESRD patients from 9 dialysis units in Northeastern Ohio
- 75% African Americans

<table>
<thead>
<tr>
<th></th>
<th>2728 Form Diagnosis</th>
<th>Criteria Diagnosis</th>
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<tbody>
<tr>
<td>Schlessenger</td>
<td>36.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>AASK</td>
<td>43.9%</td>
<td>13.5%</td>
</tr>
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</table>

### Clinical to Morphological Correlations

#### Multi-linear Regression Modeling of Morphology by Clinical Parameters

<table>
<thead>
<tr>
<th>N = 62 renal biopsies</th>
<th>Urine Protein</th>
<th>Mean BP</th>
<th>Creatinine</th>
<th>Age</th>
</tr>
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<tbody>
<tr>
<td>Glomerulosclerosis</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Obsolescent Glomeruli</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Solidified Glomeruli</td>
<td>NS</td>
<td>NS</td>
<td>0.007</td>
<td>NS</td>
</tr>
<tr>
<td>Segmental Sclerosis</td>
<td>NS</td>
<td>NS</td>
<td>0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Interstitial Fibrosis</td>
<td>0.02</td>
<td>NS</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular Sclerosis</td>
<td>NS</td>
<td>NS</td>
<td>0.007</td>
<td>NS</td>
</tr>
</tbody>
</table>

Theories on Mechanism of Hypertensive Renal Injury

Increased BP transmitted to the glomerulus
- glomerular hyperfiltration
- glomerulosclerosis
Theories on Mechanism of Hypertensive Renal Injury

- Resistance vessel arteriosclerosis
  - Interlobular arterial disease reducing glomerular flow
  - Some argue that this *precedes* hypertension

- Interstitial damage precedes glomerular damage

- Immunologic Mediators
Animal Models of Hypertension-Induced Renal Damage

• **Dahl/Rapp Rat**
  - Genetic model of salt-sensitive hypertension followed by renal damage
  - Interlobular and pre-glomerular vascular remodeling

• **Spontaneously Hypertensive Rat**
  - Vascular and structural changes, mainly seen in the deep cortical nephron, were seen in untreated and treated rats
Animal Models: Hypertension or Kidney Disease?

• Fawn-Hooded Rat
  • Spontaneously develops focal and segmental glomerulosclerosis, hypertension and proteinuria
Other Animal Models

• 2-Kidney 1-Clip Model
  – In the unclipped kidney,
    » mild renal alterations with SBP ~160
    » malignant hypertensive changes with SBP ≥ 200 mmHg
  – Acute hemodynamic change

• Sinoaortic Denervation (Dog)
  – Very high BP, fibrosis, infiltrates and vascular damage
Genetic Susceptibility toward Renal Injury

Adapted from Churchill PC et al, J Clin Invest 100:1373, 1997
Risk of ESRD associated with Race

Hsu CY et al, Arch Intern Med 165:923, 2005
Disproportionate Risk among African Americans

- Unadjusted risk is 4 – 17-fold higher among African Americans vs White Americans
- Adjustment in prevalence/severity of HT does not explain disproportionate risk

<table>
<thead>
<tr>
<th>RR HT-ESRD (B/W)</th>
<th>Georgia</th>
<th>Maryland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted</td>
<td>11.3</td>
<td>7.4 – 9.9</td>
</tr>
<tr>
<td>+ HT-adjusted</td>
<td>5.7</td>
<td>5.6</td>
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</table>

McClellan W et al, AJKD, 12:285-90, 1988
### Racial Disparity of Hypertensive Kidney Disease


<table>
<thead>
<tr>
<th>Age of ESRD (y)</th>
<th>African Am/White Incidence Ratio</th>
<th>Hispanic/White Incidence Ratio</th>
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<tbody>
<tr>
<td>15-19</td>
<td>2.5</td>
<td>--</td>
</tr>
<tr>
<td>20-29</td>
<td>6.1</td>
<td>2.0</td>
</tr>
<tr>
<td>30-39</td>
<td>9.5</td>
<td>1.9</td>
</tr>
<tr>
<td>40-49</td>
<td>10.8</td>
<td>1.8</td>
</tr>
<tr>
<td>50-59</td>
<td>20.3</td>
<td>5.1</td>
</tr>
<tr>
<td>60-69</td>
<td>7.1</td>
<td>1.6</td>
</tr>
<tr>
<td>70-74</td>
<td>4.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Understanding Health Disparities

Genetic/Biologic Background

Physical Environment

Social Environment

HEALTH OUTCOMES
Apolipoprotein 1 (APOL1) Gene Variant

- Prevents African Sleeping Sickness
- Increases Kidney Disease
Protection against African trypanosominal infection leads to a common genetic polymorphism in African Americans (12%)
Geographic Variation of APOL1

## APOL1 Renal Phenotypes

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Odds Ratio</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Gen. Population</td>
<td>--</td>
<td>12-14%</td>
</tr>
<tr>
<td>HIV Nephropathy</td>
<td>29</td>
<td>72%</td>
</tr>
<tr>
<td>Focal Segmental Glomerulosclerosis</td>
<td>17</td>
<td>72%</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>7.3</td>
<td>--</td>
</tr>
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Adapted from Kopp, Curr Opin Nephrol Hypertens 22:266, 2013
**APOL1 in the AASK Cohort**

- African American Study of Kidney Disease and Hypertension (AASK)
  - 1094 African Americans with presumed hypertensive nephrosclerosis
  - 3 X 2 RCT studying BP goal and anti-hypertensive agents
**APOL1 in the AASK Cohorts**

**A** APOL1 Risk Variants

- Patients Free from Primary Outcome (%)
  - Year: 0 2 4 6 8 10
  - 0 copies of APOL1 risk variants
  - 1 copy of APOL1 risk variants
  - 2 copies of APOL1 risk variants

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>0 APOL1 variants</th>
<th>1 APOL1 variants</th>
<th>2 APOL1 variants</th>
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<tr>
<td></td>
<td>234</td>
<td>225</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td>299</td>
<td>283</td>
<td>254</td>
</tr>
<tr>
<td></td>
<td>160</td>
<td>151</td>
<td>114</td>
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**B** APOL1 Risk According to Proteinuria Status

<table>
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<tr>
<th>P=0.16 for interaction</th>
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<tbody>
<tr>
<td>APOL1 low risk, no proteinuria</td>
</tr>
<tr>
<td>APOL1 high risk, no proteinuria</td>
</tr>
<tr>
<td>APOL1 low risk, proteinuria</td>
</tr>
<tr>
<td>APOL1 high risk, proteinuria</td>
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</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>APOL1 low risk, no proteinuria</th>
<th>APOL1 low risk, proteinuria</th>
<th>APOL1 high risk, no proteinuria</th>
<th>APOL1 high risk, proteinuria</th>
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<tr>
<td></td>
<td>399</td>
<td>392</td>
<td>375</td>
<td>339</td>
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<td>134</td>
<td>116</td>
<td>87</td>
<td>61</td>
</tr>
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<td></td>
<td>83</td>
<td>81</td>
<td>72</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>70</td>
<td>42</td>
<td>24</td>
</tr>
</tbody>
</table>

APOL1 in the AASK Cohorts

No. at Risk  | Year | APOL1 low risk, standard | APOL1 low risk, intensive | APOL1 high risk, standard | APOL1 high risk, intensive
--- | --- | --- | --- | --- | ---
263 | 0 | 260 | 79 | 81
258 | 1 | 255 | 79 | 80
246 | 2 | 254 | 73 | 76
222 | 3 | 253 | 62 | 61
151 | 4 | 252 | 30 | 39

No. at Risk  | Year | APOL1 low risk, ACE inhibitor | APOL1 low risk, other | APOL1 high risk, ACE inhibitor | APOL1 high risk, other
--- | --- | --- | --- | --- | ---
224 | 0 | 221 | 66 | 94
218 | 1 | 215 | 66 | 93
212 | 2 | 211 | 61 | 88
204 | 3 | 203 | 57 | 66
133 | 4 | 132 | 36 | 33

APOL1 in the CRIC Cohorts

• Longitudinal study of chronic kidney disease
  – Focused on progression of kidney and cardiovascular disease

• Diverse observational cohort including a variety of kidney diseases
APOL1 in the CRIC Cohorts

APOL1 Susceptibility Follows the Kidney Transplant

Lee BT, Am J Transplant 12:1924-2012
**APOL1 Mechanism of Renal Injury**

- Is hypertensive nephropathy mis-diagnosed APOL1-related disease?
- Unknown mechanism and triggers
Effects of APOL1 Variants

• Increased ApoL1 localization within the media of renal arterioles in patient with CKD
  – Madhavan SM et al, JASN, 2011;22:2119

• ApoL1 circulating levels do not correlate with genotype, CKD status and other variables
  – Bruggeman LA et al, JASN, 2014;25:634
Does Hypertension Cause ESRD?
Summary

- Severe hypertension causes renal injury leading to ESRD
- Kidney disease contributes to the development and maintenance of hypertension
- No clear evidence to support non-malignant hypertension as a cause of nephropathy
- Once CKD is present, uncontrolled hypertension accelerates progression
- Genetic Susceptibility (APOL1) plays a role in kidney disease disparities among African Americans
Nephrotic Syndrome Study Network