The Effects of Kidney Disease on the Brain: an Epidemiological Perspective

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Minesh Khatri
Internal Medicine R1
What does this... ... have to do with this?
Background

- Patients with end stage renal disease (ESRD) have an increased burden of vascular disease.

- In fact, they have up to **30 times increased risk** of adverse vascular events as compared to the general population.

- In recent years, **moderate** chronic kidney disease (CKD) has emerged as an **independent risk factor** for vascular disease as well.

- Our goal was to study the effects of CKD on cardiovascular disease, particularly stroke, in a multi-ethnic cohort.
# Stages of Chronic Kidney Disease

Table 12. Definition and Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>With Kidney Damage*</th>
<th>Without Kidney Damage*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With HBP**</td>
<td>Without HBP**</td>
</tr>
<tr>
<td>≥90</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60–89</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>30–59</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>15–29</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>&lt;15 (or dialysis)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Shaded area represents chronic kidney disease; numbers designate stage of chronic kidney disease.

* Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
** High blood pressure is defined as ≥140/90 in adults and >90th percentile for height and gender in children.

“May be normal in infants and in the elderly.

Source: K/DOQI (www.kidney.org)
Previous Studies

• Cardiovascular Health Study  (Fried, et al. JACC 2003)
  – Increased risk of CVD death (adjusted HR 1.63)
  – Increased risk of CVD (adjusted HR 1.54)
  – Increased risk of CHF (adjusted HR 1.92)

• British Regional Heart Study  (Wannamethee SG, et al. Stroke 1997)
  – Subjects > 90th percentile for creatinine at increased risk of stroke (adjusted RR 1.6)

• Inconsistencies reported with stroke
  – Often “lumped in” with other CV events
**Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.**

<table>
<thead>
<tr>
<th>Estimated GFR</th>
<th>Death from Any Cause</th>
<th>Any Cardiovascular Event</th>
<th>Any Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 ml/min/1.73 m²†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>45–59 ml/min/1.73 m²</td>
<td>1.2 (1.1–1.2)</td>
<td>1.4 (1.4–1.5)</td>
<td>1.1 (1.1–1.1)</td>
</tr>
<tr>
<td>30–44 ml/min/1.73 m²</td>
<td>1.8 (1.7–1.9)</td>
<td>2.0 (1.9–2.1)</td>
<td>1.5 (1.5–1.5)</td>
</tr>
<tr>
<td>15–29 ml/min/1.73 m²</td>
<td>3.2 (3.1–3.4)</td>
<td>2.8 (2.6–2.9)</td>
<td>2.1 (2.0–2.2)</td>
</tr>
<tr>
<td>&lt;15 ml/min/1.73 m²</td>
<td>5.9 (5.4–6.5)</td>
<td>3.4 (3.1–3.8)</td>
<td>3.1 (3.0–3.3)</td>
</tr>
</tbody>
</table>

Racial Considerations

- Racial differences exist in progression of kidney disease – African-Americans progress to ESRD faster
- AAs have much higher rates of ESRD than whites, with only ~ 50% of the additional risk being accounted for by modifiable risk factors and socioeconomic status (Tarver-Carr ME, et al. JASN 2003)
- Few studies have looked at the interaction between race, kidney function, and vascular disease
  - Especially in Hispanics
NORTHERN MANHATTAN STUDY
Prospective Cohort


BASELINE ASSESSMENT
Medical and neurological history
Risk factor assessment
Neurological exam
Fasting bloods
Echocardiography

Annual Follow-up
Annual Telephone, Hospital Surveillance

n = 3298
801 Blacks
1730 Hispanics
688 Whites

Stroke MI Death

RLS 02.05
Methods

• Creatinine clearance was determined by the Cockcroft-Gault formula:
  • Male CCl = (140 - age) x (weight) / (sCr x 72)
  • Female CCl = (140 - age) x (weight) x 0.85 / (sCr x 72)
  • CCl > 60 mL/min was reference

• Outcomes:
  – Stroke (ischemic + intracerebral hemorrhage)
  – Combined vascular events (stroke, MI, vascular death)

• Multivariate Cox proportional hazards models were constructed

• Mean follow-up time was ~ 6.5 years
## Results

**Stroke (ischemic + intracerebral hemorrhage)**

- 201 events

<table>
<thead>
<tr>
<th>Renal Marker</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>1.95 (1.48 – 2.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CCl (15 – 60 mL/min)</td>
<td>1.43 (1.02 – 2.02)</td>
<td>&lt;0.040</td>
</tr>
</tbody>
</table>

** Adjusting for age, gender, race, high school education, hypertension, diabetes, history of cardiac disease, LDL, smoking status, alcohol consumption

Results

• In race-stratified multivariate analyses, African-Americans had a RR of 2.65 for stroke, and a RR of 1.59 for combined vascular events (p < .05)

• Also, there was no significant relationship between CKD and either stroke or combined vascular events in Hispanics or Caucasians

Question:

If kidney disease can cause strokes, what other effects could it have on the brain??
White Matter Hyperintensities

- Often found incidentally on T2-weighted imaging
- Unclear pathophysiology – cardiovascular risk factors?
- Associated with increased risk of stroke, cognitive decline, and dementia (Vermeer et al, Stroke 2003; Swan et al, Neurology 1998; Vermeer et al, NEJM 2003)
CKD and White Matter Disease

- Methods: cross-sectional, MRI subgroup from Northern Manhattan Study (NOMAS), multivariate linear regression
- 615 subjects total
- Kidney function assessed using creatinine clearance, MDRD eGFR, and serum creatinine
- Outcome variable: continuous white matter hyperintensity volume
### CKD and White Matter Disease

<table>
<thead>
<tr>
<th>Estimated eGFR</th>
<th>Parameter Estimates (95% CI)</th>
<th>P – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–60 mL/min</td>
<td>0.322 (0.080 – 0.564)</td>
<td>0.009</td>
</tr>
<tr>
<td>60–90 mL/min</td>
<td>0.027 (-0.117 – 0.171)</td>
<td>0.711</td>
</tr>
<tr>
<td>&gt;90 mL/min</td>
<td>Ref</td>
<td></td>
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<tr>
<td>15–60 mL/min</td>
<td>0.322 (0.095 – 0.550)</td>
<td>0.005</td>
</tr>
<tr>
<td>60–90 mL/min</td>
<td>0.152 (0.004 – 0.301)</td>
<td>0.044</td>
</tr>
<tr>
<td>&gt;90 mL/min</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
</table>

**adjusted for age, gender, race-ethnicity, and high school education, hypertension, diabetes, cardiac disease, tHcy

Biological Plausibility

Postulated Mechanisms:

• Traditional cardiovascular risk factors
• Endothelial dysfunction
• Oxidative stress
• Uremic toxins (ADMA) (Valkonen et al, Lancet 2001)
  – Inhibits NO synthesis (powerful regulator of cerebral blood flow)
• Inflammation (i.e. homocysteine)
What Else??

We have evidence that CKD is associated with both white matter disease and stroke ...
CKD and Cognition

- Dementia has a huge emotional and economic cost to society, and is highly prevalent in ESRD population
- Identification of risk factors may provide targets for intervention
- Alzheimer’s and vascular dementia are leading causes
- Limited studies show an association between CKD and cognitive impairment
CKD and Cognition

- Methods: NOMAS cohort, longitudinal study, repeated annual assessments of cognition
- 2,172 subjects total
- Kidney function assessed using creatinine clearance, est GFR, and serum creatinine
- Outcome variable: change in Telephone Interview for Cognitive Status (TICS) score over time
## CKD and Cognition

<table>
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<th>Estimated eGFR</th>
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<th>P – value</th>
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<tr>
<td>15–60 mL/min</td>
<td>0.320 (0.232 – 0.407)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60–90 mL/min</td>
<td>0.159 (0.103 – 0.216)</td>
<td>0.005</td>
</tr>
<tr>
<td>&gt;90 mL/min</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
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<th>Parameter Estimates (95% CI)</th>
<th>P – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–60 mL/min</td>
<td>0.365 (0.291 – 0.439)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60–90 mL/min</td>
<td>0.196 (0.138 – 0.254)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;90 mL/min</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
</table>

** Adjusted for age, gender, race, insurance status, hypertension, diabetes, total homocysteine, alcohol consumption, smoking status, and history of cardiac disease

*Source:* Khatri M, Nickolas TL, Moon Y, Sacco RL, Wright CB. (In preparation)
Conclusions

- Kidney disease is a growing epidemic with far-reaching consequences
- CKD is an independent risk factor for cardiovascular outcomes including stroke
- CKD may also be an independent risk factor for white matter disease and cognitive impairment
- The impact of CKD on the CNS is only beginning to be understood and needs more research
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• Columbia University
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  – Bernadette Boden-Albala
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  – Ann-Marie Schmidt

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  – Pascal Goldschmidt
  – Deb Schwinn

• Sarnoff Endowment
Limitations (every study’s got them)

• Formulaic estimation of kidney function
• No urinary protein
• One time point for kidney function
• Cross-sectional design (white matter)
• Power issues
Possible Mechanisms

• Patients with renal insufficiency have…
  – Increased levels of inflammatory compounds
  – Abnormal apolipoprotein levels
  – Increased homocysteine
  – Abnormal coagulation
  – Anemia
  – Left ventricular hypertrophy
  – Abnormal calcium homeostasis
  – Extracellular volume overload
Limitations

- One measure of creatinine only
- No urinary protein
- Creatinine clearance and especially creatinine are relatively insensitive markers of renal dysfunction
- Results may not be generalizable to all Hispanics
- Study may be underpowered to detect race interaction
Prevalence of Renal Insufficiency

Table 19. Prevalence of Albuminuria by Age Group: NHANES III

<table>
<thead>
<tr>
<th>Albumin/Creatinine Ratio</th>
<th>20–39</th>
<th>40–59</th>
<th>60–69</th>
<th>≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>93.1% (0.6)</td>
<td>89.9% (0.7)</td>
<td>81.8% (1.4)</td>
<td>69.8% (1.3)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>6.6% (0.6)</td>
<td>9.1% (0.6)</td>
<td>16.2% (1.2)</td>
<td>26.6% (1.2)</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>0.4% (0.1)</td>
<td>1.0% (0.2)</td>
<td>2.0% (0.4)</td>
<td>3.7% (0.5)</td>
</tr>
</tbody>
</table>

This table shows prevalence of albuminuria detected in a single spot urine test.

Abbreviation: SE, standard error

Source: K/DOQI (www.kidney.org)
Prevalence of Renal Insufficiency

- **NHANES III**
  - **MDRD**
    - Age 60-69: 8% with GFR b/w 15 – 60 mL/min
    - Age 70+: 26% with GFR b/w 15 – 60 mL/min
  - **Cockcroft-Gault**
    - Age 60-69: 10% with GFR b/w 15 – 60 mL/min
    - Age 70+: 49% with GFR b/w 15 – 60 mL/min

- **NOMAS (Cockcroft-Gault)**
  - Age 60-69: 14% with GFR b/w 15 – 60 mL/min
  - Age 70+: 56% with GFR b/w 15 – 60 mL/min
Definitions

• ESRD – government terminology for Medicare payment purposes
  – Includes everyone on dialysis or renal transplant regardless of GFR
• Kidney failure – either GFR < 15 or dialysis for decreased GFR

Source: K/DOQI (www.kidney.org)
When do you Start Dialysis?

Source: K/DOQI (www.kidney.org)
Renal Insufficiency – Cause or Effect?

Renal Dysfunction

Vascular Disease (atherosclerosis, arteriosclerosis)

Inflammation, HTN, Homocysteine, LVH, anemia, etc.

HTN, dyslipidemia, alcohol

age, race, sex, smoking, diabetes, inflammation (?)
Northern Manhattan Study

Principal Investigator: Ralph L. Sacco, MS MD

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Project Managers
Janet DeRosa, MPH
Edison Sabala

Co-Investigators
B. Boden-Albala, DrPH
Ji Chong, MD
Mitchell Elkind, MD MS
M. Paik, PhD
Tanja Rundek, MD PhD
Clinton Wright, MD MS

Fellows
Lee Birnbaum, MD
Jennifer Frontera, MD
Richard Temes, MD

Research Assistants
Maria Santiago C. Mora-McLaughlin
Analisa Calderon
Sam Cammack
Sandino Cespedes, MD
Kristen Coates
Tania Corporan
Julissa Diaz, MD
Palma Gervasi
Luisa Godoy
Roman Gomez, MD
Joanna Guzman, MD
Juan Rivolta, MD
Susanna Silverman
Meghan Spyres

Data Manager
Xiaodong Luo, BS

Statistical Programmer
Hye-Seung Lee, MS

Cardiologists
Marco Di Tullio, MD
Shunichi Homma, MD

Lipid Specialist
Henry Ginsberg, MD

Administrative Ass’ts
Mary Hall
Charlene McLean
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