Cognitive Function in Dialysis

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Outline

• Epidemiology of ESRD
• Cognitive burden in dialysis
• Mechanism for cognitive decline
• Comparison of HD with PD
• Summary
Growing dialysis population

2019 USRDS ANNUAL DATA REPORT

Figure 9: Trends in the (a) crude and standardized incidence rates of ESRD, and (b) the annual percentage change in the standardized incidence rate of ESRD in the US population, 1980-2017

(a) Incidence rate per million/year
Growing dialysis population

Figure 11: Trends in the (a) crude and standardized prevalence of ESRD, and (b) annual percentage change in the standardized prevalence of ESRD, in the US population, 1980-2017

(a) Prevalence per million
Aging dialysis population

Data Source: USRDS 2018 Annual data report. Special analyses, USRDS ESRD Database. Incidence standardized to the sex-race distribution of the 2011 US population. Special analyses exclude unknown age, sex, and unknown/other race. Abbreviation: ESRD, end-stage renal disease.
Aging in dialysis and cognition

• The dialysis population is growing
• The highest growth is in older adults age 65+ years
• Older adults are already at risk for physical and mental decline
• Patients on dialysis can suffer from even greater cognitive impairment
High cognitive burden in hemodialysis

- Study evaluating cognitive function in over 300 HD patients in the Minneapolis area demonstrated over two-thirds had moderate to severe cognitive impairment
- Significantly more than the age-matched control group.

Murray AM et al, Neurology. 2006 Jul 25;67(2) 216-23
Changes in cerebral structure in HD

- Increased infarcts
- Increased atrophy
- More white matter disease
Changes in cerebral structure in HD

- 30 HD pts compared to 30 controls
  - matched with age, gender, HTN, cardiac disorder, DM
- MMSE score 22.9±4 vs 29.7±1.4
- 24 HD patients met criteria for dementia based on cognitive tests

Table 2
MRI findings in CHD patients and controls. WMH = white matter hyper-intensities.

<table>
<thead>
<tr>
<th></th>
<th>Patients (30)</th>
<th>Controls (30)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Cortical atrophy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>15</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>moderate-severe</td>
<td>2</td>
<td>4</td>
<td>n.s.</td>
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<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Ventricular atrophy:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>none</td>
<td>7</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>moderate-severe</td>
<td>8</td>
<td>2</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>7</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>punctate</td>
<td>13</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>early confluent</td>
<td>10</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>Infarcts</td>
<td>5</td>
<td>0’</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lacunes</td>
<td>14</td>
<td>4</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Importance of maintaining cognition

• Cognitive ability is important
  • for safety
  • for maintaining IADLs
  • for maintaining activity level
  • decreased risk of hospitalizations and institutionalization
  • decreased mortality
    • HD patient with dementia have half the two-year survival compared to non-demented counter parts
  • maintenance of quality of life
Outcome of cognitive impairment in HD

- Higher mortality
- Lower quality of life
- Increased hospitalizations and hospital days
- Worse nutritional state

Survival curve for all-cause mortality for patients with and without diagnosed dementia, adjusted to the mean 60 years

Kurella M, NDT, Volume 21, Issue 9, September 2006, Pages 2543–2548
Mechanism of cognitive decline

Comorbid risk factors
- Ageing
- HTN
- DM2
- Atherosclerosis

Kidney disease
- Inflammation
- Vascular calcification (impaired Ca/Phos regulation)
- Anemia

Impaired Clearance
- Uremia
- Protein accumulation
- Abnormal nitric oxide level
- Acidosis

Vascular disease and endothelial dysfunction

Stroke
Micro-infracts
White matter disease
Microbleeds
Atrophy

neurotoxic

Demyelination
Gliosis
Protein deposition

Brain Injury and Cognitive Dysfunction
Addition of HD to risk factors

Wolfgram DF, J Am Soc Nephrol Nov 2019, 30 (11) 2052-2058
Intradialytic cerebral ischemic events

As the mean arterial BP decreased during dialysis the number of cerebral ischemic episodes increased, some asymptomatic

MacEwan et al, J Am Soc Nephrol August 2017, 28 (8) 2122-2132
Intradialytic reduction in cerebral blood flow

Findlay M et al, J Am Soc Nephrol, January 2019 30 (1) 147-158

Figure 1. Haemodialysis related decline in cerebral mean flow velocity. The change in MFV during dialysis session (n=82), is presented as a median value and IQR (error bars). TCD recordings were taken prior, during, and after completion of dialysis, demonstrating a significant decline in MFV after dialysis; weighted GEE P<0.001.
Intradialytic reduction in cerebral blood flow

Polinder-Bos et al, J Am Soc Nephrol, April 2018, 29 (4) 1317-1325
Mechanisms of cognitive decline

• Renal associated causes
  • Anemia
  • Electrolyte disturbances
  • Uremia

• Comorbid associated causes
  • DM2
  • HTN

• Dialysis associated causes
  • Hemodynamic leading to changes in cerebral blood flow
    • Compare to peritoneal dialysis
Peritoneal Dialysis

• Daily dialysis that avoid rapid swings in blood pressure, electrolytes and osmolarity
• Demonstrated to preserve residual renal function compared to HD
  • Brain and kidney have similar high flow and autoregulation
• Improved quality of life
• Allows for more daytime activities, helping preserve function
Dementia onset in HD vs PD

![Graph showing the cumulative incidence of dementia over time on dialysis for HD and PD patients.]

**TABLE 5**
Dementia Risk in Each Analytical Model

<table>
<thead>
<tr>
<th>Groups</th>
<th>Analysis</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial PD vs initial HD</td>
<td>Unadjusted (Model 1)</td>
<td>0.46</td>
<td>0.41–0.53</td>
</tr>
<tr>
<td>Initial PD vs initial HD</td>
<td>Adjusted for demographics (Model 2)</td>
<td>0.64</td>
<td>0.56–0.73</td>
</tr>
<tr>
<td>Initial PD vs initial HD</td>
<td>Adjusted for all baseline predictors (Model 3)</td>
<td>0.75</td>
<td>0.66–0.86</td>
</tr>
<tr>
<td>Initial PD vs initial HD</td>
<td>Stratified propensity score</td>
<td>0.76</td>
<td>0.66–0.86</td>
</tr>
<tr>
<td>Initial PD vs initial HD</td>
<td>Matched propensity score</td>
<td>0.76</td>
<td>0.64–0.86</td>
</tr>
<tr>
<td>Initial PD vs initial HD</td>
<td>Matched propensity score, &gt;67 years</td>
<td>0.76</td>
<td>0.64–0.90</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis.

The hazard ratio for risk of incident dementia is shown comparing patients who started on PD with those who started on HD. Model 1 is unadjusted. Model 2 is adjusted for baseline demographics: age, race, gender, and primary cause of renal disease. Model 3 is adjusted for the variables from Medical Evidence Form 2728 listed under methods. Propensity scores are based on variables from Medical Evidence Form 2728 and adjusted for baseline demographics.
Cognitive changes in HD vs PD

**Table 3.** Comparison of cognitive test results at baseline and change over 1 year between those on HD and those on PD

<table>
<thead>
<tr>
<th>Test</th>
<th>HD patients (median, IQR)</th>
<th>PD patients (median, IQR)</th>
<th>p value Mann-Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit symbol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.00 (15.0)</td>
<td>40.00 (18.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Change at 1 year</td>
<td>1.00 (8.5)</td>
<td>−0.50 (8.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Trails (B-A)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>41.30 (45.15)</td>
<td>44.00 (39.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>Change at 1 year</td>
<td>−5.00 (28.3)</td>
<td>2.80 (24.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Digit span backwards</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.00 (1.0)</td>
<td>4.00 (2.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Change at 1 year</td>
<td>0.00 (2.0)</td>
<td>0.00 (2.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>FAS verbal fluency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.00 (16.0)</td>
<td>32.00 (14.0)</td>
<td>0.65</td>
</tr>
<tr>
<td>Change at 1 year</td>
<td>1.00 (9.0)</td>
<td>−1.00 (7.0)</td>
<td>0.27</td>
</tr>
</tbody>
</table>


Summary of cognitive changes in HD vs PD

- Not clear cut, but overall more in favor of greater cognitive decline and dementia risk in HD
- Difficult to compare these two patient populations with varying degree of comorbidities
Potential model

Underlying Comorbidities

- DM
- HTN
- Age

Sequelae of kidney disease

- Anemia
- Uremia
- Calcification from bone mineral disease

HD-process

- Hemodynamic instability and ischemic injury

Cerebral lesions and CI in PD

More cerebral lesions and greater CI in HD
Prevention

• Can HD-ischemic injury be mitigated
  • Dialysate cooling demonstrated to reduce BP fluctuations and reduce cerebral changes
  • Change to favoring other dialysis modalities
    • PD
    • Nocturnal (extended 8-hour HD session)
    • Home hemodialysis (more frequent session)

• Identify the patients who would be most at risk
  • Diabetics, vascular disease, older age
  • Pre-screen to measure cerebrovascular function
  • Use information in treatment recommendations
Frequent Daily and Nocturnal HD on Cognition

### Conventional vs 6x per week daily HD

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Effect Measure</th>
<th>Estimated Standardized Effects, 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Mini Mental Score</td>
<td>+ Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Trail Making B</td>
<td>- Log OR</td>
<td></td>
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<tr>
<td>Trail Making A</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Digit Symbol Substitution (DSS)</td>
<td>+ Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Pegboard Dominant Hand</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test immediate recall</td>
<td>+ Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test delayed recall</td>
<td>+ Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Letter Number Sequencing (LNS)</td>
<td>+ Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Controlled Oral Word Association Test (COWAT)</td>
<td>+ Mean Δ</td>
<td></td>
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</tbody>
</table>

### Conventional vs 6x per week nocturnal HD

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Effect Measure</th>
<th>Estimated Standardized Effects, 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Mini Mental Score</td>
<td>+ Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Trail Making B</td>
<td>- Log OR</td>
<td></td>
</tr>
<tr>
<td>Trail Making A</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Symbol Digit Coding (SDC)</td>
<td>+ Mean Δ</td>
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<tr>
<td>Rey Auditory Verbal Learning Test immediate recall</td>
<td>+ Mean Δ</td>
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</tr>
<tr>
<td>Rey Auditory Verbal Learning Test delayed recall</td>
<td>+ Mean Δ</td>
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<tr>
<td>Letter Number Sequencing (LNS)</td>
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<td></td>
</tr>
<tr>
<td>Controlled Oral Word Association Test (COWAT)</td>
<td>+ Mean Δ</td>
<td></td>
</tr>
</tbody>
</table>
Dialysate cooling
Prevention

• Need more info on nocturnal and frequent HD
• Need more info on dialysate cooling
• Need more info on PD
• Identify the patients who would be most at risk
  • Diabetics, vascular disease, older age
  • Pre-screen to measure cerebrovascular function
  • Use information in treatment recommendations
Caring for those with cognitive impairment

• Try to simplify medication regimens
  • Remove meds that can lead to more confusion (anti-histamines, anti-cholinergics)
  • Periodically check to see if meds help, stop if not helping

• Include caregivers in discussions on diet and importance of medications
  • Providing written instructions/handouts for patient to take home

• Consider dangers if medications not taken correctly
  • Risk of side effects by double dosing

• Treat the patient's symptoms over lab numbers

• Consider quality of life in changes to dialysis prescriptions
Summary

• Cognitive impairment is common and severe in dialysis patients
• Cerebral structural changes consistent with ischemic injury are common in HD patients
• Hemodialysis patients may have a higher risk of dementia and cognitive decline compared to peritoneal dialysis
• HD risk may be associated with reduction in cerebral perfusion during HD
• Pre-determining patients at highest risk for cerebral hypo-perfusion may be useful in dialysis decision making and counseling
• Increasing options with other dialysis modalities may help reduce cognitive decline
Questions?