Neurocognitive development in children with ESRD

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Disclosures

- none

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Learning objectives

- Learn about the current state of research on neurocognitive development in children with ESRD
- Learn about prevalence and etiology of neurocognitive delays in pediatric ESRD patients
- Identify screening techniques and interventions for neurocognitive difficulties

Background

- neurodevelopmental dysfunction in children with chronic kidney disease (CKD) is well recognized as ***significant comorbidity***
- neurocognitive deficits include difficulties in language, visual-spatial ability, memory, and executive functioning (eg attention)
- Neurocognitive domains are critical for information acquisition, understanding, retention in medical, social, educational settings

CKD impact on functioning

- Difficulties with adherence
  - Attention to parental commands
  - Remembering complex medication regimens
  - Following inevitable (and sometimes frequent) changes to regimens
  - Self-monitoring daily medical routines
- Coping with stress of chronic medical condition
  - Limited cognitive resources
  - Reduced QOL
  - Increased risk for mental health problems

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Possible risk mechanisms

- **Physiological:** advanced uremia and anemia may alter brain metabolism and neuronal myelination and synaptic development (e.g., uremia, anemia, HTN, seizures)
- **Environmental:** CKD treatment regimens disrupt school attendance and compromise academic achievement; impaired sleep hygiene (~59%)
  - Chronic school absenteeism ($\geq$18d/yr): 17% CKD vs 2.7% gen

(Chen et al., 2018; Davis et al., 2012; Richardson et al., 2018)

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Domains of interest

- **Intellectual functioning (IQ):** reasoning, solving problems
  - Verbal & nonverbal reasoning, processing speed
- **Executive functioning (EF):** regulating cognitive processes
  - Memory, attention, learning, self-control, self-awareness
- **Academic functioning:** acquiring academic skills and knowledge
  - Academic achievement
  - Learning disorders

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EVIDENCE-BASED ASSESSMENTS

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Assessment tools

- IQ tests: standardized, administered tests
  - Wechsler Intelligence Scales
  - Standford-Binet
  - Kaufman
- Executive Function
  - Administered tests (e.g., WRAML, DKEFS, CPT)
  - Rating scales (e.g., BRIEF): parent, teacher, self reports
- Academic achievement
  - WJ, WRAT, WIAT

REVIEW OF STUDIES

Meta-analysis: neurocog/acad outcomes for youth with CKD (Chen et al., 2018, Clinc J Am Soc Neph)

- Overall: 34 studies, total n=2095
- Full Scale IQ (FSIQ) avg lower than healthy controls
  - All CKD (n=758) -10.5 points
  - Mild-mod CKD (n=582) -9.39
  - Dialysis (n=23) -16.2
  - Transplant (n=153) -11.2
- CKD/txp 10-11 pts higher than dialysis

Meta-analysis: neurocog/acad outcomes for youth with CKD (Chen et al., 2018, Clinc J Am Soc Neph)

- CKD lower than healthy controls on:
  - Executive function (EF): attention
  - Verbal and visual memory
  - Academic skills in math, reading, spelling

Meta-analysis: neurocog/acad outcomes for youth with CKD (Chen et al., 2018, Clinc J Am Soc Neph)

- Adv stage CKD < mild-mod CKD: IQ, memory
- Duration of reduced kidney function, rather than age of onset → worse memory & acad skills
- Children on dialysis may be at greatest risk… *but also constitute the smallest portion of sample analyzed*

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IQ & EF after txp in early childhood (Qvist et al., 2002)

- Sample: n=33 txp @<5yo (h/o PD), M f/u 6yrs later
- Method: IQ (WISC-R), EF (NEPSY)
- Results:
  - Mean IQ = 87.5 (range 65-118)
    - 42% avg IQ, 42% low avg/borderline, 9% extremely low (ID/MR)
  - EF: 25% reduced attention span
  - Placement: 79% normal class, 21% special edu
- **Conclusion:** majority of patients functioning well, but clear evidence of negative academic impact

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Peds CKD and EF, memory
(Gipson et al., 2006, Child neuropsychology)

- Sample: n=20 CKD (M age=13.4yo, 50% male, 50% White, 60% dialysis) vs n=19 controls (M age=12.9yo, 50% male, 67% White)
- Method: memory (WRAML), problem-solving (TOL), attn (Gordon CPT), verbal fluency (COWA), visual-spatial fluency (Ruff), working memory (WJ), IQ (WASI)
- Results: *CKD assoc with greater working memory deficits*
  - Control > CKD: IQ, memory (WRAML-all subtests), EF (initiation, sustaining)
  - CDK = controls: verbal learning, picture memory, visual learning
- **Conclusion:** CKD youth may benefit from multiple repetitions, and immediate, direct feedback to enhance understanding

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IQ and acad ach in ped CKD
(Duquette et al., 2007)

- Sample: ped CKD (n=30, 50% dialysis) vs controls (n=41), 6-18yo
- Method: IQ (WASI), acad ach (WIAT), learning problems
- Results:
  - Controls > CKD: verbal IQ, nonverb IQ, overall IQ; acad ach reading, math)
  - CKD > controls: low achievement in reading, math, spelling
  - <u>Grade retention: 40% CKD, 2.4% controls</u>
  - <u>IEP: 16.7% CKD, 2.4% controls</u>
  - GFR sig predictor of IQ/acad ach (~47% variance explained)

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CKiD: mild-mod CKD & neurocog functioning (Hooper et al., 2011)

- Sample: n=386 (26% FSGS, 74% structural urologic disease; 59% male, 69% White, 18% LBW) vs asthma (n=61) and seizures (n=43)
- Method: disease severity (iGFR, elev proteinuria), IQ (WASI), attention (CPT-II), EF (parent BRIEF), and acad ach (WIAT)
- Results:
  - high iGFR → better EF, acad skills
  - elev prot → lower IQ, verbal IQ, attn probs
- **Conclusion:** most mild-mod CKD have normal cog fxn, but 20-40% showed dysfunction >1 SD

Systematic review: neurocog outcomes of ESRD, ESLD, CF, & hemophilia A (Moser et al., 2013, peds anesth)

- Groups chosen to represent low cog risk (CF), moderate risk (ESRD, Ns=14-62), high risk (hem A, ESLD)
- ESRD & ESLD: mild cog deficits (more than CF, hem A), with improvements associated with transplant
- ESRD: renal txp improves cog function:
  - post-dialysis (Mendley & Zelko, 1999; Rasbury et al., 1983)
  - at/before age 30mo pre/post txp (Davis et al., 1990)

ESRD during infancy: neurocog/acad outcomes
(Johnson & Warady, 2013, Peds Neph)

- Method: ESRD <16mo (n=12, M age 11yo) v healthy sibs (n=9, M age 10yo)
- Results:
  - – ESRD: lower IQ, EF, acad ach
  - – More months on dialysis = lower IQ, slower processing speed
  - – Younger age at txp = better processing speed, working memory, EF, acad ach
- **Conclusion:** limit time on dialysis and transplant as young as possible?

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CKiD: CKD duration and EF (Mendley et al., 2014)

- Sample: n=340 (61% male, 83% White), ages 6-21yo
- Method: eGFR, CKD duration, attn (CPT-II), EF (DKEFS)
- Results:
  - – 22% had IQ<85, 35% EF probs ($\geq$1 SD below mean)
  - – Longer CKD duration → worse inhibitory control, vigilance (attn)
  - – All other areas were not related to CKD duration, and no findings related to eGFR
- **Conclusion:** disease duration important for EF

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Neurocog dysfxn in youth with CKD
(Ruebner et al., 2016 Am Jrl Kid Dis)

- Sample: CKiD cohort (n=92) vs controls (n=70)
- Results:
  - CKD < Controls: attention, memory (verbal, visual, working, short-term), inhibitory control
  - Higher eGFR assoc w/ trend better performance: attn, visual-spat memory
  - Lower pm diastolic dipping = worse attention
- **Conclusion:** monitor ABPM and manage BP; possible role of disease severity predicting cognitive outcomes

Clinical predictors of neurocog deficits in CKD
(Slickers et al., 2007, Pediatr Nephrol)

- Sample: n=29 (M age=12.5yo, 52% male, 48% ESRD)
- Method: disease severity (eCr/Cl), CKD duration, CKD comorbidities, IQ (WASI), attention (Gordon CPT), memory/learning (WRAML)
- Results:
  - High eCr/Cl → better IQ, memory
  - Higher CKD duration yrs → worse memory
  - Sub-group analysis: younger age at CKD onset, more % life CKD → lower IQ
- **Conclusion:** disease severity important risk factor

INTERVENTIONS FOR COGNITIVE FUNCTIONING IN CKD

Renal transplantation
(Icard et al., 2010; Mendley & Zelko, 1999)

- CKD: effects of kidney filtration on cognitive status
- Hypothesis: transplant improves filter and cognitive fxn
- Method: examination of cognitive functioning before and after transplant
- Small samples, but preliminary results…

Improvement in EF after renal transplant (Mendley & Zelko, 1999)

- Sample: n=9 ESRD; pre/post txp
- Results:
  - Pre/post txp improvement: attention, working memory
  - No change: focal attention, verbal learning, visual-spatial perception, motor speed
- **Conclusion:** improvements in motor-free decision speed

Cognitive improvement in CKD after transplant (Icard et al., 2010, pediatr transpl)

- Sample: n=6 txp, n=20 CKD no txp, n=23 controls
- Results:
  - Txp=IQ boost
  - But…txp group < CKD no txp group at T1 (& = at T2)

Table 1. Composite IQ/developmental scores over time (mean = 100, s.d. = 15)

Group	Time 1	Time 2
CKD – Transplant	72.83 (19.95)	85 (19.04)
CKD – No Transplant	87.15 (17.78)	83.55 (23.58)
Control	115.13 (16.49)	118.13 (15.13)

Scores represent a combination of the Mullen Early Learning Composite and the WASI Full-4 IQ.

- **Conclusion:** txp helps but does not normalize cognitive functioning

Cognitive remediation?
(Javalker, Ferris, Cuttance, & Hooper, 2017)

- CR = behavioral intervention to improve cognition
  - e.g., working memory, attention, EF
- Variable efficacy with pediatric populations (e.g., ADHD, intellectual disabilities)
- Possible targets for ESRD: attention, working memory, processing speed

Special education and school supports

- Individualized Education Plan (IEP)
- Access to tutors, extra support
- Baseline and follow-up neuropsychological evaluations
- Monitoring of academic achievement, progress
- Educational testing for learning impairments

Psychologist involvement

- Neurocognitive and psychoeducational testing
- Assessment/treatment of emotional and social problems
  - Peer concerns, mood, anxiety
- Promoting optimal parent management of child behavior
- Monitoring quality of life to target interventions appropriately
- Supporting medical team interventions to promote optimal communication and adherence to recommendations

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General conclusions

- Variable effects of disease severity/duration, but clear negative association between CKD/ESRD and cognition
- Renal transplantation may alleviate risk in older children
- Cognitive deficits improve but persist after transplant
- Dialysis may pose unique risk, but data are limited

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Clinical Recommendations

- Regular neuropsychological assessments
  - Baseline assessment of neurocog functioning at time of diagnosis?
- Advocacy for IEP/special education supports (OHI, LD)
- Reducing emotional distress that may influence functioning at school
- Addressing absenteeism effects related to school, reducing effects of school disruptions
- Optimizing treatment engagement/adherence

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Research gaps

- Incidence of learning disorders, IEP use
- Relationship among treatment type, absenteeism, and cognitive/learning problems
- Variable link btw disease severity and neurocog functioning – perhaps different measures of disease severity needed?
  - Effects of medical comorbidities on cog status?
- Best school practices for supporting pediatric CKD patients

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Thank you!

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