Implications of Treatment for ALL on Attention, Memory & Learning

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A Brief History of Time in Pediatric ALL Treatment
  CRT vs Contemporary Protocols

Meet Jason

Different ways of looking at outcome
  IQ
  Attention: Performance, Rating, Cognitive neuroscience
  Memory

Implications for everyday life

Looking ahead
Times they are a changing

ALL IS MOST PREVALENT OF CANCER DIAGNOSES AMONG
CHILDREN WORLDWIDE AT 26.8% (KAATCH 2010)

Then

- Cranial radiation therapy (CRT) + intensive chemo
  - 5 yr EFS of 80% in SR-ALL
  - Marked neurocognitive deficits
  - Impacts HRQoL & daily function
    Speechley et al 2006; Huang et al 2013

BUT...

Paradigm Shift

- Contemporary ALL protocols
  - 93.5% overall survival rate
    Pui et al 2009

BUT...

- Late effects include cardiovascular, endocrine morbidities
- Impact better understood over past 5 - 10 years
More than ever before…

Discovery that the brain should be treated proactively saved lives.

5-Year Relative Survival Rate for Acute Lymphoblastic Leukemia

Data obtained from Surveillance, Epidemiology, and End Result Program (SEER)
## Impact

### CRT
- IQ (up to 15 point decline)
- Attention
- Memory
- Processing speed
- Academic/vocational attainment
- HRQoL

### Contemporary Chemo
- CNS-directed therapy $\rightarrow$ methotrexate (MTX)
- High-dose systemic & IT MTX
- Impact is more subtle
  - Variability
    - Cohorts
    - Designs

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Comparison of Long-Term Neurocognitive Outcomes in Young Children With Acute Lymphoblastic Leukemia Treated With Cranial Radiation or High-Dose or Very High-Dose Intravenous Methotrexate

Brenda L. Spiegler, Kimberly Kennedy, Ronnen Maze, Mark L. Greenberg, Sheila Weitzman, Johann K. Hitzler, and Paul C. Nathan

2006
Meet Jason

- Diagnosed with ALL in 2001
  - just under age 3 years

- Treatment included:
  - Intrathecal methotrexate
  - High dose IV MTX with leukovorin rescue in first interim maintenance
  - 2.5 years of systemic chemotherapy

- Underwent regular neuropsychological assessment
  - ages 5, 10, 13 & 17.5
Contemporary ALL protocols & Neurocognitive Change

**Design**

- **Cross sectional**
  - Spiegler et al., 2006; Kadan-Lottick et al., 2010; Krull et al., 2013; Edelmann et al. 2014; Kanellopoulos et al. 2016

- **Longitudinal**
  - Active treatment → post-treatment survivorship phase
    - Harila et al., 2009; Halsey et al., 2011; Jacola et al., 2016
  - CRT vs. chemo-only
    - Harila et al., 2009; Krull et al., 2013
  - Chemo-only vs. controls
    - Walsh et al., 2015; Kanellopoulous et al. 2016

- **Cohort size**
  - N = 10-50
    - Harila et al., 2009, Edelmann et al., 2014
  - N > 100+
    - Kadan-Lottick et al., 2010; Krull et al., 2013; Jacola et al, 2016; Walsh et al. 2015
Where do we stand on IQ?

- **Declines in general intelligence over time**  
  Halsey et al., 2011; Iyer et al., 2015

- **Decline in verbal intelligence**
  - End of Tx, 5 yrs post-Tx & 10-32 years post-Tx  
  Harila et al., 2009

- **No declines**  
  Spiegler et al. 2006; Kanellopoulos et al. 2016; Zeller et al. 2013

- **Devil is in the details**
  - Core cognitive domains & underlying processes
Attention

- Performance tasks
  - "objective" performance compared to age-based norms
  - Trails, DKEFS, Wechsler Digit Span, Stroop, Conners CPT

- Rating Scales
  - Subjective ratings provide proxy or self-raters
  - Conners3, BRIEF

- Cognitive neuroscience paradigms
  - Discrete cognitive processes associated with underlying neurological function
    - N-back (working memory)
    - Stop Signal Reaction Task (response inhibition)
Attention

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Attention

- N=167 survivors
- 2 years post-Tx
  - Survivors = normative expectations
    - IQ, academics, learning & memory
  - Survivors at higher risk for attention problems
    - < norms for sustained attention
    - Younger age at Dx predicted higher risk
  - Attention problems at end of treatment
    - predicted lower academic scores 2 years post
N = 567  (N= 214 chemo-only)
Mean age = 33 yrs
Mean Time Since Dx = 26 yrs

Wechsler digit span, Conners CPT

High rates of severe impairment (more than expected population mean of 2%)
  - Executive function (15.9%)
  - Attention (14.5%)
Attention

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  - Subjective ratings provide proxy or self-raters
  - e.g. Conners3, BRIEF

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  - Discrete cognitive processes associated with underlying neurological function
    - N-back (working memory)
    - Stop Signal Reaction Task (response inhibition)
Examined inter-rater agreement

- Multiple raters on attention questionnaire for adolescent survivors (39 BT & 41 ALL) – 1 yr post Tx
- Conners-3 & CPT

Results:
- Parents & teacher – moderate agreement
- Variable btw self & proxy
- Inattention subscale associated w/ omission errors
256 SR ALL vs. 256 HC

BRIEF (Gioia et al. 2000)

Overall EF comparable
  - Flexible thinking
  - Independent initiation

Subset of survivors impaired
  - Cognitive flexibility
  - Emotional control
  - Initiation
  - Working memory

Older age at testing predicts greater EF problems (WM & self-monitoring)

Subtle challenges emerging over time
Behavioural Control & Coping

Executive Function, Coping, and Behavior in Survivors of Childhood Acute Lymphocytic Leukemia* 2009

Laura K. Campbell,1 PhD, Mary Scaduto,2 BA, Deborah Van Slyke,3 PhD, Frances Niarhos,3 PhD, James A. Whitlock,3 MD, and Bruce E. Compas,3 PhD

1University of Virginia Health System, 2Ohio State University Medical Center, and 3Vanderbilt University

Highlights importance of ongoing monitoring of multi-modal aspects of EF and impact across areas – performance, ratings, environments


The Impact of Attention on Social Functioning in Survivors of Pediatric Acute Lymphoblastic Leukemia and Brain Tumors

Katherine H. Moyer, MA,1 Victoria W. Willard, PhD,2 Alan M. Gross, PhD,1 Kelli L. Netson, PhD,3 Jason M. Ashford, MS,2 Lisa S. Kahalley, PhD,4 Shengjie Wu, MS,5 Xiaoping Xiong, PhD,3 and Heather M. Conklin, PhD2*
Attention

- Performance tasks
  - "objective" performance compared to age-based norms
  - Trails, DKEFS, Wechsler Digit Span, Stroop, Conners CPT

- Rating Scales
  - Subjective ratings provide proxy or self-raters
  - Conners3, BRIEF

- Cognitive neuroscience paradigms & neuroimaging
  - Discrete cognitive processes associated with underlying neurological function
    - N-back (working memory)
    - Stop Signal Reaction Task (response inhibition)
Smaller volumes of cortical grey matter, cerebral white matter, amygdala, caudate*, hippocampus, thalamus & est. intracranial volume  Zeller et al. 2013

Treatment-related white matter volume associated with performance on EF tasks  Reddick et al. 2014; Reddick et al. 2006

Male ALL survivors’ poor N-back & SSRT performance associated with altered brain morphology  Van der Plas 2016
Activation levels

ALL survivors = HC during “low” levels of N-back

ALL survivors > HC
• “high” levels of N-back

Fig. 1. Between group differences in DLPFC activation on the 2 versus 0 N-back contrast during neuroimaging. Differences in activation in the 2-back versus 0-back conditions for survivors of ALL (left column) and control subjects (right column). Yellow-to-orange clusters indicate areas of significantly greater activation in the 2-back condition relative to the 0-back conditions. Red circles identify the bilateral region of interest (right and left DLPFC).
Memory & Learning

- When identified, **verbal memory deficits** are most consistently reported Harila et al 2009; Krull et al 2013

- Emerging challenges with EF likely impact ability to attend to and learn new material

- Implications for academics, social function
- N = 567  (N= 214 chemo-only)
- Mean age = 33 yrs
- Mean Time Since Dx = 26 yrs
- High rates of severe impairment (2SD < mean) than expected population mean of 2%
  - Executive function (15.9%)
  - Attention (14.5%)
  - Memory (13.1%)
What does it all mean?

Evidence is in
- Most consistent findings:
  - Executive Function
  - Attention
  - Working Memory
  - Verbal memory
  - Processing speed

May impact
- Academic attainment
- Psychosocial function
- May not manifest until adolescence & adulthood
  - Increased demand for efficiency, independence & inferential thinking
Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Cancer Survivor Study


- N=1560
- Survivors w/ & w/o CRT
- Chemo-only (N=752)
- Increased (vs. sibling control)
  - Behavioural
  - Social
  - Learning challenges
- Increased parent-ratings of
  - Inattention-hyperactivity
  - Social withdrawal
  - Headstrong behavior
- Associated with Special Ed & reduced adult educational attainment

Figure 2: Effect of cognitive and behaviour problems on reduced attainment of college education in survivors with and without CRT

Figure shows data from Poisson regression. CRT=cranial radiation therapy.
Dose-related neurotoxicity

- HD MTX (more than 1 g/m²) < LD MTX Aukema et al. 2009, Krull et al., 2013

- Cumulative doses of IV MTX ↑ risk for slowed processing
  - 3% for each 1 g/m² Krull et al. 2013

- Dose-response association
  - IV MTX & inattention-hyperactivity symptoms Jacola et al. JCO 2016
  - Also reported as part of CCSS study Jacola et al. 2016
Genetic Polymorphisms

- Folate-related genetic polymorphisms are related to attention outcomes. (Krull et al., 2008; Kamdar et al., 2012)

- Strong relationship btw MTHFR polymorphisms & inattentive Sx in ALL survivors.
Jason revisited

- Diagnosed with ALL in 2001 - just under 3 y/o

- Treatment included:
  - Intrathecal methotrexate
  - High dose IV MTX with leukovorin rescue in first interim maintenance
  - 2.5 years of systemic chemotherapy

- Underwent regular neuropsychological assessment
  - ages 5, 10, 13 & 17.5

- Academic challenges
- Behavioural regulation issues
- Mood?
Memory (2015)

Mean = 100, SD - 15

- Verbal Imm
- Verbal Del
- Visual Imm
- Visual Del
**Behavioural Ratings**

**Conners -3: Parent**

- Inattention
- Hyper-Impul
- Exec Function

**BRIEF: Parent**

- Behav Reg
- Metacognition
- Composite

*Higher = More difficulty*
Jason at 17

- Core intelligence generally intact
- Slow to get written work done but good “hands on”
- Variable attention and working memory
- Parental endorsement of inattentive and impulsive behaviours
- Struggling to cope with academic demands

- Moved to co-op placement for grade 12
- Connected with SAVTI – applying for apprenticeship program
Greater than sum of its parts

- Accounting for discrepancy of findings
  - Assessment approach (IQ, academics vs attention & EF)
  - Treatment (types, dose intensities, administration route)

- Description & quantification of prevalence

- Underlying pathophysiologically processes

- View towards early detection & preventive measures
Individual variability

Disease

Genome

Environment

Drug

Cheung & Krull, 2015
Individual variability

Genome

Disease

Chronic health condition

Drug

Environment

Cheung & Krull, 2015
Customization of Survivorship Care

- Genetics
- Phenotyping
- Neuroimaging
- Biomarkers
- Physiological

Dx & pre-treatment phase, active treatment, survivorship and post-treatment phase of treatment
Thank you