Bone Marrow Failure Disease and The Brain

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Center for Brain Health
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GOALS:
1. Discuss the types of cognitive problems that patients experience and how those problems are related to the functioning of different brain networks and systems.
2. Explain the process of neuropsychological evaluation and describe how it may be helpful for an individual who is dealing with cognitive symptoms.
3. Describe the (very limited) scientific literature regarding the nature and causes of these problems.
4. Provide suggestions for coping with these problems on a day-to-day basis.

Cognitive Functions

What is ‘Cognition’
• All of the skills of thought
  – Memory
  – Concentration
  – Language Skills
  – Visual Skills
  – Executive Functions
    • Reasoning & Problem Solving
    • Judgment
    • Impulse Control
    • Flexibility
    • Planning
    • Sequencing and Organizing

Movement and Coordination

• Quantify speed and dexterity
• Adds a quantitative element to examination of movement
• Tests progress from proximal/gross to distal/fine
  – Grip strength
  – Finger tapping
  – Grooved pegboard

Visuospatial

• “Where” pathway (blue)
  – Visual search
  – Location of objects in space
• “What” pathway (yellow)
  – Object identification
  – Facial recognition
• Integration/construction
  – Image rotation
  – Drawing
  – Block design
Prosopagnosia

Language

- Language Production
  - Fluency
  - Phrase Length
  - Prosody
- Naming (Word Finding)
- Comprehension
- Reading
  - Word recognition
  - Comprehension
- Writing

Memory

Recent memory:
- Encoding
  - Bringing information into memory system
  - Highly related to attention
  - Depends on focus and processing speed
- Storage (Consolidation)
  - Retention of information over time
- Retrieval
  - Ability to recall the specific details later
  - Use recognition paradigm (yes/no) to disentangle retrieval from consolidation based memory deficits.
Neuropsychological Evaluation: Attention, Processing Speed & Working Memory

- Attention
  - Sustained Attention
  - Divided Attention
  - Shifting Attention
- Working Memory = mental RAM
  - Information you “hold in mind”
  - Has a maximum capacity
  - Sets limits on amount of material you can process at one time
- Speed of processing is related to attention
  - Processing automatic material is rapid
  - Interference occurs between competing information
  - “Multi-tasking”

Executive functions
- “Frontal lobe” tests
- Reasoning & problem solving
- Inhibition
- Shifting
- Initiation, cessation, perseveration
- Requires integration of other domains, efficiency
- Other qualitative executive skills
  - Awareness/insight
  - Judgment

Memory
- Recent memory

Processing Speed

Sustained attention/working memory

Stroop Color Word Test

<table>
<thead>
<tr>
<th>Practice 1</th>
<th>Practice 2</th>
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<tbody>
<tr>
<td>Trial 1</td>
<td>Trial 2</td>
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read word

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Name color of X's

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Name color of font

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| Blue | Red   | Green|
| Green| Red   | Blue |
| Blue | Green | Blue |
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| Red  | Blue  | Red  |
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Personality/emotion

- Clinical interview
- Standardized measures
  - Mood measures (BDI, BAI, Hamilton, etc)
  - Personality measures (PAI, MMPI)

Phineas Gage

- "The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is . . . irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires . . . obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others. . . ." (John Harlow, MD, 1868)

Phineas Gage

Damasio et al., Nature 1994

How common are cognitive problems in bone marrow failure disease

- All studies to date use combined samples
- Include individuals with MDS along with more common conditions such as Acute or Chronic myelogenous leukemia (AML or CML)
  - In a study of 106 patients with either CML (n=91) or MDS (n=15), ~25% had low scores on one or more cognitive test at the time of diagnosis (Meadows et al., 2013).
  - The %age of people with low test scores improved at 18 months after treatment (15%).
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How do bone marrow failure diseases affect cognition?

Anemia and cognition

- Low blood hemoglobin levels can lead to decreased oxygen to the brain
- In a sample of 88 patients with AML (n= 41) or MDS (n=47), hemoglobin levels were correlated with neuropsychological test scores (Wood et al, 2011).
  - Used cutoff scores:
    - Mild anemia = 10-12.5 mg/dl
    - Moderate = 8-10 mg/dl
    - Severe = < 8 mg/dl

Wood et al, 2011

- Those with mild anemia had no relationship between Hgb and cognitive performance.
- Moderate – Severe anemia led to decreased performance on tests of recent memory, working memory, and fine motor speed.
  - 25% of patients with mod-sev anemia were had impairments on multiple tests in this battery

Anemia

- Fatigue
  - Results in a reduction in arousal
    - <Attention
    - <Working Memory
    - <Processing speed
  - People experience a memory problem
    - Due to reduced encoding

Meyers et al., 2005

- Gave neuropsychological tests to 54 people with AML (n=19) or MDS (n=35) before chemotherapy
  - 26 returned for follow-up testing 1 mo after treatment
- Age: Average = 60 years (range = 21-84)
- Gender: 30 male/24 female
- Response: (1 month)
  - Complete = 19 (14 seen for follow up)
  - Partial or no response = 23 (8)
  - Not evaluated = 12 (4)
- Hypothesized that these symptoms may have to do with cytokine-immunologic activation.

Other causes of Cognitive Impairment in MDS (& AML)

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Cognitive Sequelae of Chemotherapy

- The concept of 'chemobrain' is controversial
- Chemo agents damage the white matter
  - Brain’s fibers of connection
  - Reduces attention, processing speed (encoding), working memory

Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Interferon-alpha
  - Increases the level of interleukins and TNF-alpha
  - Related to problems with memory, motor dexterity, problem solving, and mood
  - These increased cytokine levels are caused by MDS/AML
  - Treatment with multi-agent chemotherapy increases them

Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Cognitive domains tested:
  - Attention
  - Speed of Information Processing
  - Recent Memory
  - Cognitive Flexibility
  - Motor Dexterity

- Other areas assessed:
  - Activities of daily living
  - Fatigue
  - Quality of Life

Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Biological variables
  - Levels of various Cytokines in blood
    - Interleukins 1, 6, 8
    - Tumor Necrosis Factor – Alpha
    - Hemoglobin levels

Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Risk factors for cognitive decline:
  - Some agents are more neurotoxic than others
  - Method of delivery (intrathecal)
  - Age
  - Total dose
  - Vascular risk factors (diabetes)
  - Genetic polymorphisms/individual factors?
    - Apolipoprotein E (APOE)
    - Brain derived neurotrophic factor (BDNF)
    - Catecholamine-o-transferase (COMT)
    - C-reactive Protein (CRP) ... and others

Meyers et al., 2005

- Results
  - Before treatment, > 40% had low performance on 1 test
  - Cognitive function declined 1 month after treatment

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<th>Test</th>
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<th>Follow-up</th>
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Scientific studies of Cognitive Impairment in MDS (& AML)

- Take home points
  - The rate of cognitive problems is somewhere from 25-45% at disease onset
  - Hgb levels <10 mg/dl may increase the likelihood of cognitive symptoms and fatigue
  - There is also a relationship between cytokine levels and cognitive symptoms
  - Fatigue did not have as strong a relationship with cognitive test scores as did cytokine levels
  - Cognitive symptoms may get worse during treatment (e.g., at 1 month), but seem to improve after treatment is complete and recovery occurs (e.g., 12-18 months).

Maintaining Brain Health

- Does brain ‘exercise’ help?
  - It’s better than nothing…
  - …but not necessarily better than anything else
  - Cognitive “exercise” improves performance on the specific tasks
    - Attention related activities
    - Semantic network type activities
  - Generalizability of results mixed
  - Buyer beware

Maintaining Brain Health

- Physical exercise
  - Helps promote overall brain health
  - Improves blood flow to the brain
  - Can help reduce the loss of brain with aging
  - Talk to your doctor about the level of exercise that is safe
  - General guidelines are similar to those for heart health

Maintaining Brain Health

- Cognitive Rehabilitation
  - Compensatory strategies are most effective method
    - Identify the goal you’d like to achieve or the thing you’d like to do better.
    - Work with someone to develop a strategy to achieve that goal
    - Cognitive rehabilitation specialists
      - Speech therapy
      - Occupational therapy
    - Success is contagious!

The value of exercise

Kramer et al., 2011, PNAS
Maintaining Brain Health

- Compensatory strategies are most effective method
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Summary

- The brain is not considered a primary site of pathology in AA, MDS and PNH
  - Despite that, many factors combine to affect brain function and cognition in some people with these disorders
- Primary issues include fatigue, immune system processes, chemotherapy side effects
- Treatment for cognitive problems is available:
  - maintaining good general brain health
  - developing strategies on an individual basis
  - Some medications can help
- Neuropsychological evaluation and cognitive rehabilitation are useful to understand the cause of a cognitive problem and develop strategies to deal with it

Questions?