Bone Marrow Failure Disease and The Brain

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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.

Bone Marrow Failure Disease and the Brain

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
How do aplastic anemia, MDS and PNH effect cognition?

• Anemia and related Fatigue
• Immune Response Activity
• Complications (infections, encephalitis, epilepsy)
• Treatment
  • Chemotherapy
  • Hematopoietic Stem Cell Transplantation

The Cognitive Functions:

Intelligence

• General intellectual functioning
  – Wechsler Intelligence Scales (WAIS-IV, WISC-IV), Stanford-Binet
  – Current tests divide general IQ into 4 subscales
    1. Verbal comprehension (vocabulary, similarities, comprehension)
    2. Perceptual organization (block design, matrix reasoning, Picture Completion)
    3. Working memory (Digit Span, letter-number sequencing)
    4. Processing speed (Digit-symbol, Symbol search)
  – Concept of a general factor (g): There is some core genetic factor that captures much of intelligence (“it’s hard to define, but I know it when I see it”)

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
    - Getting the information in – highly related to attention
    - Depends on focus and processing speed
  - Storage (Consolidation)
    - Free recall of information after a delay/distractor interval
    - % retention
    - Depends on hippocampus
  - Retrieval
    - Use recognition paradigm (yes/no) to disentangle retrieval from consolidation based memory deficits.
Memory
Recent memory

Attention, Processing Speed & Working Memory

- Working Memory = mental RAM
  - 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
  - Simple vs. complex
  - Multi-tasking

Processing Speed
Sustained attention/working memory

Practice 1

Trial 1

Practice 2

Trial 2

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

Stroop Color Word Test

<table>
<thead>
<tr>
<th>Read Word</th>
<th>Green</th>
<th>Blue</th>
</tr>
</thead>
<tbody>
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<tr>
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<tr>
<td>Green</td>
<td>Blue</td>
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Name color of X’s

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XXX  XXX  XXX
XXX  XXX  XXX
XXX  XXX  XXX
XXX  XXX  XXX
XXX  XXX  XXX
XXX  XXX  XXX

Name color of font

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

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

Phineas Gage

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)
Anemia and related Fatigue
• Immune Response Activity
• Complications
• Cancer Treatment
  – Chemotherapy
  – Hematopoietic Stem Cell Transplantation

How do aplastic anemia, MDS and PNH effect cognition?

Anemia
• Fatigue
  – Results in a reduction in arousal
    • Attention
    • Working Memory
    • Processing speed
  – People experience a memory problem
• In severe anemia, low hemoglobin can result in hypoxemia in the brain, very rare.

Scientific study of Cognitive Impairment in MDS (AML)
Meyers et al., 2005 Cancer 104:788-793
Many people with cancer have problems with memory, fatigue, and depression. Treatment often worsens these symptoms. The symptoms may not go away after treatment is finished. These symptoms may have to do with cytokine-immunologic activation.

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

Gave neuropsychological tests to 54 people with AML/MDS before chemotherapy
– 26 returned for follow up testing 1 mo after treatment
• Age: Average = 60 years (range = 21-84)
• Gender: 30 male/24 female
• Diagnosis:
  – Myelodysplastic syndrome = 35
  – Acute Myelogenous Leukemia = 19
• Response: (1 month)
  – Complete = 19 (14 seen for follow up)
  – Partial or no response = 23 (8)
  – Not evaluated = 12 (4)
Scientific study of Cognitive Impairment in MDS (& AML)
Meyers et al., 2005 *Cancer;* 104: 788-793.

• 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

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

• Results
  – Before treatment, many people had cognitive symptoms
  – The rate of symptoms increased after treatment

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline (n = 50)</th>
<th>Follow-up (n = 20)</th>
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<tbody>
<tr>
<td>Attention</td>
<td>7</td>
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<tr>
<td>Psychomotor speed</td>
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<tr>
<td>Verbal recall</td>
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<td>56</td>
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<tr>
<td>Immediate recall</td>
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<td>15</td>
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<tr>
<td>Digits recall</td>
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<td>18</td>
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<tr>
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<tr>
<td>Eyes-open</td>
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<td>4</td>
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<tr>
<td>Dexterity</td>
<td>15</td>
<td>5</td>
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</tbody>
</table>
Scientific study of Cognitive Impairment in MDS (& AML)
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- Take home points
  - There is a strong relationship between cytokine levels and cognitive symptoms
  - Fatigue did not have as strong a relationship with cognitive test scores as did cytokine levels
  - In fact, some patients showed improving cognition during chemotherapy when tumor necrosis factor alpha levels went down

Cognitive Sequelae of Chemotherapy

- 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

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

A 'frontier'?
Maintaining Brain Health

Does brain ‘exercise’ help?
- It’s better than nothing…
- …but not necessarily better than anything else
- Buyer beware

Medications
- Attention enhancers
- Memory enhancers

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**

- The value of exercise

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**Hippocampus**

Erickson et al., 2011, PNAS

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**Maintaining Brain Health**

- 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!

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**Frontiers**

- Individual difference variables that predict cognitive outcomes
  - e.g., APoE alleles and immuno marker as mediators of risk
  - Functional neuroimaging
- Methods of neuropsychological assessment
  - Increasing sensitivity
  - Computerized
Summary

• The brain is not considered a primary site of pathology in AA and MDS
• Despite that, many factors combine to effect brain function and cognition
• Primary issues include fatigue, Immune system processes, chemotherapy side effects
• Treatment for cognitive problems is best accomplished by maintaining good general brain health and developing strategies on an individual basis
• Neuropsychological evaluation is a useful way to understand the cause of a cognitive problem and develop strategies to deal with it

Questions?