Radiation-Related Fatigue: Phenotyping, Pathogenesis, Treatment

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Chief, Symptoms Biology Unit
Division of Intramural Research, NINR
Objectives

At the end of this presentation, we will:

• Define radiation-related fatigue (RRF)
• Describe an approach to phenotype RRF
• Enumerate the methodological approaches utilized in RRF investigations
• Identify recently developed therapeutics for RRF
State of the Nursing Science

- Increasing need to address the aging population and the long-term impact of chronic illnesses
- Addressing the health care needs of a diverse Nation
- Shifting emphasis from treatment to prevention
- Increasing reliance to technology
Develop knowledge to improve quality of life:

• Build scientific foundation for clinical practice
• Prevent disease and disability
• Manage / eliminate symptoms caused by illness
• Enhance end-of-life and palliative care
4 Key Themes Guiding the Implementation of the NINR Strategic Plans

1. Symptom Science: Promoting Personalized Health Strategies
2. Wellness: Promoting Health and Preventing Illness
3. Self-Management: Improving Quality of Life for Individuals with Chronic Illness
4. End-of-Life and Palliative Care: The Science of Compassion
National Institute of Nursing Research

Director: Patricia A. Grady, PhD, RN, FAAN
Deputy Director: RADM (ret) Ann Knebel, PhD, RN, FAAN

Division of Extramural Science
- Biobehavioral Branch
  - Cardiovascular Symptoms Unit

Division of Intramural Research
- Symptom Management Branch
  - Genomic and Clinical Biomarkers Unit
- Tissue Injury Branch
  - Symptom Biology Unit

Scientific Director:
Ann Cashion, PhD, RN, FAAN
Focus Areas:

• Nature and causes of fatigue in a variety of specific conditions including cancer

• Symptoms associated with fatigue

Purpose: Identify functional pathways for potential therapeutic intervention including lifestyle changes.
1. Define fatigue related to cancer or cancer treatment (e.g. Radiation Related Fatigue [RRF])

2. Describe a method to phenotype RRF.

3. Identify genomic and proteomic approaches to pursue discovery of biomarkers for RRF.

4. Develop clinical trials to target the identified biomarker.

Cashion & Grady, 2015
Unmet Needs for Improved Fatigue Management

• Up to 96% of patients with cancer experience fatigue

• No clear case definition of cancer-related fatigue (e.g. RRF).

• Clinical management of fatigue is compromised because the etiology of CRF remains elusive.

  ▪ CRF is associated with negative health outcomes including depression, impaired cognitive function, sleep disturbance, and decreased health-related quality of life (Byar et al., 2006).
Definition and Clinical Guidelines

ICD-10 criteria for CRF

Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is (A1) significant fatigue.

A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
A2. Complaints of generalized weakness or limb heaviness
A3. Diminished concentration or attention
A4. Decreased motivation or interest to engage in usual activities
A5. Insomnia or hypersomnia
A6. Experience of sleep as unrefreshing or nonrestorative
A7. Perceived need to struggle to overcome inactivity
A8. Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued
A9. Difficulty completing daily tasks attributed to feeling fatigued
A10. Perceived problems with short-term memory
A11. Postexertional malaise lasting several hours

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatoform disorder, somatoform disorder, or delirium.

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NCCN guideline

Non-pharmacologic
• activity enhancement
• psychosocial interventions
• attention-restoring therapy
• nutrition
• sleep therapy

Pharmacologic
• attention restoring agent
**Design:** prospective, descriptive, observational study

**Methods:** questionnaires, computerized cognitive tests, portable hand-grip test, physical activity monitor, blood
Fatigue During Radiation Therapy

Clinical Study (NCT00852111)

- Inflammation (e.g. *IFI27*)
- Neuroprotection (e.g. *SNCA*)

\[ N=45 \]

\[ *p<.05, **p<.001 \]

Low scores = High fatigue
Fatigue During Radiation Therapy

Clinical Study (NCT00852111)

N=45

![Graph showing mean fatigue scores over time points]

- **p<.001

![Graph showing changes in FACT-Fatigue scores]

- Low scores = High fatigue
47 articles reviewed:

- CRF was measured using 23 different questionnaires

- Even when the same questionnaire was used, different scoring rubrics were applied to phenotype CRF
RRF Phenotyping Approaches:

A. FACT-F 43-point cutoff
   - captures fatigue experience best
   - correlated with differences in gene expression

B. FACT-F 3-point change
   - can isolate chronic fatigue

C. PROMIS-F 50 T-score cutoff
   - most sensitive to subtle changes in fatigue.
Issues with RRF Phenotyping

Principal component analyses showing differences in transcriptome profiles of the RRF phenotype using 3 different fatigue phenotyping approaches.

<table>
<thead>
<tr>
<th>Top up-regulated genes</th>
<th>Approach 1</th>
<th>Approach 2</th>
<th>Approach 3</th>
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</thead>
<tbody>
<tr>
<td>FACT-F 43-point cut-off</td>
<td>FACT-F 3-point change</td>
<td>PROMIS-F T-score &gt;50 cut-off</td>
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<td>Gene ID</td>
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<td>PROMIS-F T-score &gt;50 cut-off</td>
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<td>Gene ID</td>
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<td>CDC25C</td>
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<td>YPEL2</td>
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<tr>
<td>OLIG2</td>
<td>-1.32</td>
<td>6.91E-5</td>
<td>MTBP</td>
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</table>

GO enrichment analyses

Approach 1: 244 genes
- biological adhesion (46%)

Approach 2: 40 genes
- biogenesis (22%)

Approach 3: 21 genes
- circadian rhythm (17%)
Whole blood collected using Paxgene tube

Extracted RNA

Genomics
Supervised Classification by Filter Methods and Recursive Feature Elimination Predicts Risk of Radiotherapy-Related Fatigue in Patients with Prostate Cancer

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<table>
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<th>Symbol</th>
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<td>GRM8</td>
<td>Metabotropic glutamate receptor</td>
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<td>GRM5</td>
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<td>GRIK2</td>
<td>Ionotrophic glutamate receptor</td>
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<td>GRIK3</td>
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<tr>
<td>ARG2</td>
<td>NMDA receptor</td>
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Proteomics

Methods: 2-DIGE, LC-MS, WB, ELISA

- TRAIL (TNF-related apoptosis-inducing ligand)
- Neurometabolites (Apo-E)
- BDNF

After FDR correction (adjusted \( p \) value < 0.05)
Radiation-Induced Fatigue Mouse Model

Anesthesia

Radiated

Control

NMDAR

Glutamate receptor

Wheel Running Activity (km ± SEM)

Day

Control

Radiated

Control

Anesthesia

Radiated
Etiology of RRF

↓ synaptogenesis

↓ firing of 5-HT neurons or ↓ response to serotonin

↑ Fatigue

References:
1. Stan et al., 2014
2. Homayoun and Moghaddam, 2007
3. Meeusen et al., 2006
4. Papuc et al., 2010
5. Weyman et al., 2014
- **Purpose**: Quantify central levels of glutamate during RRF.
- **Hypothesis**: RRF is associated with decreasing glutamate signals.
- **Method**: MRS (3.0 Tesla)
**Hypothesis**: Improving fatigability will reduce overall fatigue.

**Objectives**:
1. To determine if improving fatigability will reduce RRF.
2. To measure expression and association of BDNF with levels of RRF.

**Collaborator**: NIH Clinical Center Rehab Medicine

**Exercise Intervention** (amendment to NCT00852111)

1. **Continuous training**
   – target heart rate: 60-70% more than resting

2. **High impact intensity training**
   – target heart rate: >90% more than resting
Bonferroni post hoc tests indicated significantly lower fatigue scores from 40 minutes following ketamine infusion through day 2 (p<.05).

The effect size of the ketamine-placebo difference was greatest at day 2 (d=0.59).
Title: Effect of Ketamine on Fatigue following Cancer Therapy NCT02317341

Objectives:

1. To determine the *immediate effect* of a single, IV dose of ketamine in reducing clinically-significant fatigue in individuals who completed radiation therapy for cancer.

2. To investigate the effect of ketamine on BDNF levels, markers of inflammation and mitochondrial function, as well as on cognitive function and skeletal muscle strength.
Sample and Study Design

Sample: 40 subjects who completed radiation therapy for cancer
Design: double-blind, active placebo-controlled, cross-over study

Period 1

Drug A
Ketamine 0.5 mg/kg
OR
Midazolam 0.045 mg/kg (active placebo)

Drug B
Infusion
24h phone call
NIH visit: 3d post
NIH visit: 7d post
14d phone call

Period 2

Drug A
Ketamine 0.5 mg/kg
OR
Midazolam 0.045 mg/kg (active placebo)

Drug B
Infusion
24h phone call
NIH visit: 3d post
NIH visit: 7d post
14d phone call
Ongoing Research Activities

• Clinical trials: optimizing extramural collaborations
  - Univ. of Maryland, Univ. of Florida, Georgetown, VCU

• Lab activities:
  1. RNA sequence
     - post-transcriptional modifications, mutations
     - cellular pathway alterations during radiation
  2. central versus peripheral
     - protein levels in blood versus CSF

• Animal:
  - knock-out mouse models
  - treatments that increases BDNF
Cancer-Related Fatigue (CRF)

Review: Gap in Literature
Saligan & Kim, 2012
*Brain, Behavior, Immunity*

Clinical Observation
Laboratory Investigation

↑ Health-related Quality of Life

Reduce CRF

Molecular Markers of CRF
Acknowledgement

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