Brain Radiation-Induced Fatigue is Associated with Neuroinflammation and Suppression of Orexin Signaling

Aaron J. Grossberg MD, PhD
Assistant Professor
Department of Radiation Medicine
Cancer Early Detection Advanced Research Center
Brenden-Colson Center for Pancreatic Care
Oregon Health & Science University
Nothing to disclose
Brain radiation-induced fatigue

- 200,000 patients/year
  - Brain metastasis
  - Primary intracranial tumor
  - Pediatric brain tumors

- >90% of patients report fatigue
- Cognitive impairment
- Growth Restriction
- Metabolic dysregulation
Inflammation and activity

Grossberg, Marks J Neurosci 2011

Gotter Pharmacological Rev 2012
Hypothesis

Brain radiation → Brain inflammation → Decreased Orexin release → FATIGUE

Brain radiation

Brain inflammation

Decreased Orexin release
Design

WBRT 4Gy x 5

Home Cage Locomotor Activity
Brain radiation-induced fatigue

Fatigue Onset
Day 1

Fatigue Nadir
Day 5

Fatigue Recovery
Day 11

Total Locomotor Activity

Day

XRT
WBRT 4 Gy x 5
Sham

Food Intake

Day

XRT
Sham

Food intake (g/day)

Day

Baseline
Day 1
Day 2
Day 3
Day 4

Body Weight

Day

XRT
Sham

Body mass (g)

Grossberg, Dantzer, Grosshans unpublished
Inflammatory Gene expression
Hypothalamus

Onset
Day 1

Nadir
Day 5

Recovery
Day 12

Grossberg, Dantzer, Grosshans unpublished
Brain radiation-induced fatigue

**Biology**

- **Day 1**
- **Day 5**
- **Day 12**

<table>
<thead>
<tr>
<th></th>
<th>CSF [Orexin-A] (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td></td>
</tr>
<tr>
<td>XRT</td>
<td></td>
</tr>
</tbody>
</table>

**XRT x time interaction p = .002**

Grossberg, Dantzer, Grosshans *unpublished*
Brain radiation-induced fatigue

Clinical

11 pediatric patients with brain tumors treated with RT

Pre-RT → Post-RT (2) → Post-RT (3) → Post-RT (4)

Inflammatory

Non-inflammatory

Grossberg, Dantzer, Grosshans unpublished
Brain radiation-induced fatigue

Clinical

11 pediatric patients with brain tumors treated with RT

Fatigue correlated with post-RT
- sTNFR1
- sTNFR2

Pre-RT → Post-RT (2)

Fatigued

Non-Fatigued

[Orexin-A] (pg/mL)

P = 0.026

Grossberg, Dantzer, Grosshans unpublished
Brain radiation-induced fatigue

Clinical

11 pediatric patients with brain tumors treated with RT

Pre-RT → Post-RT (2) → Post-RT (3) → Post-RT (4)

Inflammatory

Non-inflammatory

Grossberg, Dantzer, Grosshans unpublished
Brain radiation-induced fatigue

Brain radiation → Brain inflammation → Decreased Orexin release → FATIGUE
Brain radiation-induced fatigue

Questions

• Can we demonstrate causation?
• Is fatigue reversible? Is fatigue preventable?
• What are the drivers of chronic fatigue after WBRT?

Grossberg, Dantzer, Grosshans unpublished
Acknowledgements

Brain Radiation and Fatigue

Grosshans Lab
- David Grosshans
- Die Zhang
- Wei Zhou
- Connie Weng
- Thanh Lam

Dantzer Lab
- Robert Dantzer
- Elisabeth Vichaya
- Phillip Gross
- David Grosshans
- Robert Dantzer
- Elisabeth Vichaya
- Phillip Gross

Funding:
RSNA R&E Resident Research Grant