Symptom Research in Children with Cancer: One Researcher’s Journey

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Objectives

1. Share the journey of the last 22 years exploring symptoms experienced by children and adolescents during cancer treatment.

2. Describe oxidative stress measures that reflect the severity of cancer treatment symptoms.

3. Discuss future directions for continued symptom exploration.
The Journey
Searching for Evidence

- Resilience and Vulnerability
- Protective Factors
- Cancer Treatment Stressors
- Fatigue
- Sleep
- Depression
- Anemia
- Symptom Clusters

- CNS Toxicity
- CNS Tissue Injury
- Neurocognitive Function
- Measures of CNS Toxicity
  - Phospholipids
  - Fatty Acids
  - Genetic Polymorphisms
- Math Interventions
The Evidence: Vulnerability and Resiliency in Children

- Resilience acquired through competencies in the individual, family and environment
- Resilience is a process of overcoming adversity
- Vulnerability- risk of attack or damage
  - The “glass doll” analogy
    Anthony and Koupernick, 1974
Childhood Cancer Stressors

Cancer Stressors

Acute

Chronic
Childhood Cancer Stressors in Children with Cancer

Hockenberry-Eaton, Manteuffel, Bottomley, 1997

Most Frequent Cancer Stressors

- Hair Loss
- Vomiting
- Meds
- Pain
- Weight
The Evidence: Childhood Cancer

Stressors: Physical Symptoms

- Physical Stressors associated with childhood cancer
  - Tired
  - Nausea and vomiting
  - Sleep changes
  - Hair loss
Fatigue in Children with Cancer

- Established fatigue as a significant symptom in children with cancer through qualitative and quantitative research designs
- Identified the need to measure fatigue in children with cancer

ONS FIRE grant, 1996 - Hockenberry and Hinds
The Evidence: Factors Associated with Fatigue

- Sleep disturbances
- Medications
- Nausea and Vomiting
- Hospital Environment
- Mood
- Treatment phase
- Disease status
Childhood Cancer Symptoms Model

Adapted from Armstrong, 2003; Dodd and Others 2001; Hockenberry and Others, 1999; 2000

Person Factors
- Gender
- Age

Environmental Factors
- Clinic Visits
- Hospitalization

Disease Factors
- Diagnosis
- Treatment

Symptoms
- Fatigue
- Sleep
- N & V

Quality of Life
- Performance
- Behavior
- Mood
• Explore the symptom trajectory in children during their first 16 months of childhood leukemia treatment.

• Explore the influence of the oxidative stress pathway on symptom occurrence, severity, and distress during this time period, using $F_2$-Iso-P in children’s CSF to measure oxidative stress levels.
Children with cancer experience multiple symptoms resulting from the disease and its treatment. The oxidative stress pathway may play a role because:

1) High oxidative stress increases risk of cellular and tissue damage
2) Chemotherapy administered in the course of treatment promotes formation of reactive oxygen species and increases the level of oxidative stress
3) Damage occurs and leads directly or indirectly to development and/or exacerbation of chemotherapy-related symptoms
Oxidative Stress Pathway and Symptom Distress

Leukemia Treatment → Oxidative Stress

Leukemia Treatment Symptoms:
- Fatigue
- Sleep
- Pain
- Nausea
- Depression
- Physical Activity
- Cognition / Memory
During all 6 time periods, the most frequently reported symptoms (occurred in >30% of the children) were: lack of energy, pain, being irritable, nausea, feeling nervous, lack of appetite, difficulty concentrating.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Mean # of Days from Diagnosis</th>
<th># Sx Reported in &gt;30% of Children</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>11</td>
<td>Reported in &gt;50% of children: hair loss, lack of energy, pain, being irritable, sweats, and feeling of sadness</td>
</tr>
<tr>
<td>2</td>
<td>142</td>
<td>14</td>
<td>Symptoms more frequent than in T1: nausea, lack of appetite, weight loss, changes in food tastes, vomiting, mouth sores, feeling nervous, difficulty concentrating, cough</td>
</tr>
<tr>
<td>3 - 5</td>
<td>241 to 424</td>
<td>11, then 10, then 8</td>
<td># of symptoms decreased over time</td>
</tr>
<tr>
<td>6</td>
<td>510</td>
<td>6</td>
<td>The 6 symptoms were: cough, lack of appetite, being irritable, difficulty concentrating, difficulty sleeping, pain</td>
</tr>
</tbody>
</table>
Trajectory of Symptoms over Leukemia Treatment
**F₂-ISOPROSTANES AND SYMPTOMS**

- **F₂-Iso-P and Symptoms: Post-Induction Phase of Chemotherapy**
  - The highest F₂-Iso-P concentration during post-induction (at Time 3) was significantly correlated with total number of symptoms ($r = 0.528; p = 0.035$) and with mean symptom severity ($r = 0.661; p = 0.005$).
  - The highest F₂-Iso-P concentration during post-induction (at Time 3) was correlated with mean symptom distress at trend level ($r = 0.471; p = 0.066$).
RESULTS: F₂-ISOPROSTANES AND SYMPTOMS

- **F₂-Iso-P and Symptoms: Continuation Phase of Chemotherapy**
  - The highest F₂-Iso-P concentration of during continuation was significantly correlated with total number of symptoms at Time 5 ($r = 0.516; p = 0.041$) and at Time 6 ($r = 0.526; p = 0.036$).
This work is the first to reflect symptom trajectory changes over 16 months of childhood leukemia treatment and examine the influence of the oxidative stress pathway on symptom frequency, severity and distress.

Our findings contribute to the evidence that pediatric leukemia chemotherapy drugs can trigger reactive oxygen species (ROS) production as byproducts of cellular destruction.
Combining what we know about oxidative stress and symptom severity and clusters into a currently funded grant

Associating symptom severity with level of oxidative stress and presence of genetic variations in children with ALL

Exploring genetic variations associated with the oxidative stress and inflammatory pathways