Severe self-injury in developmental disorders:
*Sensory & immune findings from the periphery*

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Interagency Coordinating Committee for Autism
2016
Disclosures

None

Not an ASD expert
The Need

Good evening, my name is ______. I am typing on a phone, so excuse obvious typing issues. I am a mom to a 9 year old with autism. His repetitive head behaviors in toddler years grew into highly intense head punching a few years ago. The typography of his sibs has evolved and recently has gone back to chin and temple punching. Your name came up a year ago and many things prevented me from reaching out to a complete stranger.

Fast forward to today and I find myself in a crisis. ______ was just released from _____ on Friday with an ng tube. He refuses to eat solids......Unraveling this story is interesting, but insanity producing to us, parents. So now I have 2 major issues and depending on the day, he can be very physically aggressive too.

I could tell you so much more, but I reach out to you today in hopes you have ideas. The hospital was at a loss on how to support us as intense behavior issues are not their specialty and the pysch unit seemed really inappropriate for a young, autistic child with a new ng tube.
Parent Perspective

• Why?
• Help, please.
Scientific Puzzle & Clinical Paradox

• Why do some people with intellectual and developmental disabilities/disorders self-injure by almost any possible means without regard to the consequences? Actions that should normally be regulated by their outcome become ‘out of control’ among individuals with chronic self-injury.
Self-injury & ASD

- **Prevalence:** Estimates vary widely (8% - 72%)
  - Subgroups? (e.g. HFA vs. LFA)

- **Mechanisms:** unknown & understudied
  - We don’t understand pathophysiology

- **Interventions:**
  - Established evidence base for behavioral interventions but ...
    - Evidence for more severe cases is limited particularly wrt maintenance
  - Biomedical intervention – no consistent evidence
  - Evidence-vacuum: sad/bad things happen (restraint, sedation, aversives...)

- **Cost / burden of care:** Significant
  - Society: NIH 1998 US estimate ... ~$3 billion
  - Family: likely far exceeds impact of ASD alone
  - Person: significantly impacts quality of life
Self-injurious behavior (SIB): Some general conceptual models

• Developmental – Behavioral
  – Communication: SIB develops into a means of expressive communication in non/minimally verbal cases

• Psychological – Psychiatric
  – Linked to essentially all forms of comorbid psychiatric symptoms (irritability, anxiety, OCD, depression, hyperactivity)

• Neurological
  – Sensory / Pain: common assumption is insensitivity to pain or increased pain threshold
Self-injury & pain: Insights from animal models & pain-related neurologic conditions

• Self-injury is the standard behavioral marker of altered nociception and pain in animal models that involve damage to peripheral nerves.

• Consistent with human cases (e.g. sensory neuropathies) where damage to peripheral nerves can produce:
  - altered sensation at peripheral sites (focal → generalized)
  - “hyperalgesia” (increased sensitivity to pain) & “allodynia” (non-noxious stimuli perceived as painful)
  - self-injury targeted to site where sensation has been altered

• Inflammatory & immune-related mechanisms play a role in the development of altered nociception and neuropathic pain in both animal models and clinical conditions.

• By way of analogy think about scratch → itch or related sensory experiences you have had (e.g., sunburn)

• In all the clinical instances and preclinical models, it seems that SIB is driven by increased sensory sensitivity, NOT decreased sensitivity.
Our Overall Approach & Focus

• Pain markers in persons with cognitive / communication deficits with and without SIB
  – Sensory testing + pain biomarkers
  – SIB associated with hyperalgesia: increased sensory sensitivity + altered autonomic & immune activity
Collaborators
Supported, in part, by: NIH/NICHD (R,K) 35682;44763
McKnight Land-Grant Professorship, UMN Futures

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Self-Injury - saliva, skin, and sensory mechanisms

Saliva:
Non-invasive window; vulnerable population

Skin:
Where behavior meets biology

Sensory Mechanisms:
Thresholds – intact, altered?
Nervous System & Skin

Brain
Spinal cord
Peripheral nerve

Epidermis
Dermis
Hypodermis
How Does Experience Get Under the Skin?
"Whoa! That was a good one! Try it, Hobbs — just poke his brain right where my finger is."
Experience gets ‘under the skin’ ………through the skin
Peripheral Nervous System & Skin
...for touch/tactile and pain/nociception...

To Get to Here
You have to go through here

- Brain
- Spinal cord
- Peripheral nerve
- Epidermis
- Dermis
- Hypodermis
The skin is our body’s largest sensory organ – comprised, in part, by an array of different specialized nerve endings.....
Background – Sensory Fibers

A-alpha nerve fibers carry information related to proprioception (muscle sense)

A-beta nerve fibers carry information related to touch

A-delta nerve fibers carry information related to pain and temperature

C- nerve fibers carry information related to pain, temperature, and itch
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Normal Skin

Sensory Nerves:
- Nerve Bundles
- Sub Epidermal Neural Plexus
- Epidermal Nerve Fibers

Nerve Fiber Assessment:
- Epidermal Nerve Fibers
- Basement membrane
- Branch points and length

Epidermal Nerve Fiber Density:
- Accurate
- Objective
- Quantifiable
Bio-Behavioral Analysis of SIB, Sensory Mechanisms, and Pain
Pain perception depends on the functioning of the peripheral nerves and their ability to transmit the pain signal to the central nervous system (Ji & Woolf, 1999).

Quantitative sensory testing provides an opportunity to study indirectly peripheral nerve functional integrity (Greenspan, 2001).
Skin Biopsy Approach/Methods

• Sample to Date
  – SIB cases
    • 25 adult [80% profound cognitive impairment]/Residential
    • 5 pediatric [100% profound cognitive impairment]/Outpatient
    • 13 pediatric [global developmental delay]/Outpatient
  – No SIB with developmental disability/delay controls (N = 16/10)
  – No SIB with no developmental disability controls (N = 45 [but adult])

• 3 mm punch skin biopsy
  – SIB Group: non-self-injurious body site
  – Control: site-matched normal skin samples
  – No known primary chronic illness (e.g., diabetes) or genetic condition associated w/SIB (e.g., LNS).

• Dependent measures
  – Epidermal nerve fiber (ENF) structure: coefficient of variation (CV)
  – Peptide content: SP, CRGP, VIP
  – Immune activity: mast cell granulation
Normal Skin

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Altered Peripheral Nerve Morphology

A. Normal

B. SIB

ENFs
Epidermis
Basement Membrane
Dermal Nerve
Capillary

100 μm
Epidermal nerve fiber (ENF) density: Coefficient of variation (CV)
### Altered Neuropeptide Content

#### Density, Spacing, and Neuropeptide Content of SIB and Control Biopsies

<table>
<thead>
<tr>
<th>Forearm Biopsy</th>
<th>ENF Density</th>
<th>Gap CV</th>
<th>SP</th>
<th>CGRP</th>
<th>VIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIB 1</td>
<td>27.6</td>
<td>105</td>
<td>5</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>SIB 2</td>
<td>31</td>
<td>118</td>
<td>9</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>SIB 3</td>
<td>37.2</td>
<td>103</td>
<td>7</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>36.4</td>
<td>79</td>
<td>2.0</td>
<td>10.3</td>
<td>0</td>
</tr>
</tbody>
</table>

*5% = 17.8, N=45*
Immune Activity: Mast Cell Degranulation

Degree of granulation = Degree of Immune activity

SIB vs No SIB Controls
- $p(\text{SIB/dm}) = 0.75$
- $p(\text{CTL/dm}) = 0.23$
- $X^2 = 4.99 < 0.05$
Neuro-Immune Crosstalk: Sensory Behavioral Effects?

Frequency

Control
SIB

0 1 2 3 4

Rating

Superficial Dermis
Deep Dermis
Mast Cell Rating

0 = no degranulation
1 = degranulation in deep dermis only
2 = deep and mid-dermis degranulation
3 = degranulation throughout
4 = extensive degranulation throughout

mean FAU

SIB + MR
MR-only
Neuro-Immune Crosstalk: Sensory Behavioral Effects?


![Diagram showing sensory behavioral effects with frequency and mast cell rating data.]
So What?
Peripheral ‘pain’ biomarkers = SIB risk markers?

– initial observations of altered intra-epidermal nerve density differences in adult sample with chronic SIB (no controls)
  
  *Pain 134, 232-237.*

– replicated finding with a larger sample of adult SIB cases relative to matched controls *Brain, Behavior, & Immunity, 23, 365-370.*
  
  • observed increased SP-positive fiber counts in some but not all samples
  • observed extensive mast cell degranulation (consistent with immune mediated inflammatory response)

– also observed that adult individuals with SIB and altered peripheral markers (relative to matched controls) were more (not less) responsive during a modified quantitative sensory testing protocol *The Journal of Pain, 11, 773-781.*
Early ENFd variation w/ ‘At Risk’ sample

At Risk: ‘High’ (?) ENFd

At Risk: ‘Normal’ (?) ENFd

SIB02-012  Calf skin biopsy  ENFs/mm=209.39

SIB02-016  Calf skin biopsy  ENFs/mm=77.3
Hypothetical Plot of ENF Density Histogram

Evidence to date for extreme low and high density ENF innervation among SIB cases

(Symons et al., 2008 *Brain, Beh, & Immunity*, 23; Symons et al, 2008, *Pain*, 134.)
Coupling the impact forces with the frequency of blows during a single bout of self-injury would essentially be the equivalent of dropping a 48-oz (3-lb) hammer on your forehead every second for up to a half an hour.
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Summary of findings

• **ASD subtype** (ASD with or without IDD)
  – Clear differences in SIB phenotype
  – Severe & persistent SIB common in ASD+IDD

• **Objective methods** for measuring nociception in persons who are nonverbal
  – Quantitative Sensory Testing + FACS
  – Biomarkers

• **Altered nociceptive function** SIB in ASD+IDD findings consistent with allodynia / hyperalgesia
  – ↑ response to multiple sensory modalities suggesting that non-noxious stimuli might be perceived as painful (e.g. touch, temperature changes, etc).
  – Alterations in ENFs that could disrupt sensory/pain signaling
  – Alterations in immune-mediated inflammatory response
Clinical implications:
- **Assessment:** SIB & nonverbal pain signs
- **Intervention:** Tx pain, Tx SIB?
Research implications from mechanism to treatment target

Susceptibility Genes

Environmental Triggers

Mast Cell Mediators

Brain Inflammation

CRH NT

Neonatal stress

IL-1 IL-6 TNF

Maternal Immune Activation

LPS Poly(IC) ROS

Environmental Toxins

Mast Cell Activation

Brain Autoantibodies

Proinflammatory Cytokines

IL-6 MCP-1 TGFβ1 TNF

Peptides (NT, SP, β-endorphin)

Extracellular mtDNA

ASD subtype-specific phenotype (cognition, communication, RRB, SIB)