"Neuropathic pain: Can stress and pain itself cause a sickle crisis?"

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Sickle cell disease in an inherited red blood cell disorder.

- 240,000 children born annually in Africa with Sickle Cell disease
- 80% of these kids die by their second birthday
- Estimated 80,000 affected in USA, 6900 in Ca.
- 97% of children in the US survive to age 18
- 1/360 African Americans, 1/16,305 Hispanic
What is Sickle Cell Disease

Sickle cell anemia

- Inherited problem with red blood cells that makes them become very rigid when they release oxygen to tissue.
- Affects 1/400 people of African descent
- Rigid red cells block blood flow
- Constant damage to organs.
- Sudden episodes of terrible pain
- Results in poor quality of life and premature death
Small pneumonia can turn into fatal lung failure in hours.

Big and small strokes start in childhood and cause brain damage.

Severe painful damage to bones.

Old data we hope are changing:
- 38% have a small stroke by age 8
- 50% have blood vessel disease in their brain by age 14
- Strokes reduce IQ by 30%
- Half of SS patient pass by age 42-60
- Crisis pain is like pain from bone fracture
- Adults have pain 50% of days
- 30% of adults have pain 95% of days
- 50% of adults have chronic lung failure
- 30% of adults have chronic kidney failure
SCD Survival in Children
(Survival ≠ Normal)

- Newborn screening / Early diagnosis
- Comprehensive SCD center care
- Penicillin prophylaxis ASAP
- Immunization for encapsulated organisms
- Aggressive treatment of fever / infection
- Hydroxyurea at maximal tolerated dose for all SS/S\(\beta^0\) patients > 9 mo
- TCD screening and prophylaxis for stroke if indicated
- Consider bone marrow transplant for all SS/S\(\beta^0\) patients

Quinn et al, 2010  Blood 115(17)  3447
Vaso-occlusion

% Solidified HbS

Time

Td = Delay time

oxygen released from HbS

Tt = Transit time

Post capillary venule

Td 1

Td 2

Pre capillary arteriole

ANS

Vasoconstriction

L – Glutamine

Mental Stress
Fear
Anxiety
Pain
Cold
Respiration

NO depletion
ET-1

NO depletion
ET-1

Adhesion
Inflammation
ET-1
Viscosity
Coagulation
ANS

If Td<Tt, SS-RBCs become lodged in the microvasculature

HU

Td 1

Td 2

Flow

Flow

Vaso-occlusion

Tt = Transit time

Respiration
Bench to Bedside: Management of SCD

Increase delay time to polymer formation: Use Hydroxyurea
✓ Reduces hospitalizations by 50%
✓ Reduces hospital duration by 50%
✓ Reduces mortality in adults by 40%
✓ Reduces TCD velocity
✓ Push to max tolerated dose (around 35 mg/kg)
✓ Start HU at 9 months of age (NIH recommendation)

Blood Transfusion
✓ Dilutes out HbS RBC
✓ Improves viscosity, or at least changes it

Maintain good perfusion to improve microvascular flow
✓ Gently hydrate
✓ Keep patient warm
✓ Treat inflammation
✓ L-Glutamine
✓ Treat pain
✓ Airy-Fairy psycho treatments to calm the nerves

We do this and believe it helps but in fact, it has never really been studied
Pain is the hallmark of sickle vasoocclusive crisis.

Sickling happens continually. We really don’t know exactly what causes the sudden exacerbations or “crises”? Patients tell us cold, stress, anxiety and pain itself can trigger crisis.

It is very important to get control of severe ”crisis” pain with adequate doses of medications quickly (but)

Narcotics make you more likely to get neuropathic pain and make neuropathic pain worse.

SCD patients can have both kinds of pain at the same time.

Patients and medical providers need to know the difference between these two kinds of pain.

Anxiety, stress, lack of sleep make any kind of pain much worse.
Measurement of blood flow in response to pain caused by heat

Prefrontal cortex Oxygenation changes (fNIR)

Autonomic Parameters (HR variability and Baroreceptor reflexes)

Peripheral Blood Flow: Laser Doppler Peripheral Arterial tonometry (PAT) Pulse Oximetry

Medoc Thermal Neurosensory Analyzer (TSAII)
Could Pain Cause Changes in Regional Blood Flow?

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Task1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
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</table>

- **Pain Signal**
- **Peripheral Blood Flow (Contralateral hand)**
- **Respiration**
- **Prefrontal cortex oxygen content**

**Diagram:**
- Neural mediated vasoconstriction
- Oxygen goes to tissue
- Neutrophil platelets adhesion
- Small arteriole
- Blood flow blocked

**Graph:**
- Time (sec) from 0 to 4500
SCD patients have different response than Controls!

SCD subjects vasoconstricted faster in response to pain.

SCD subjects had stronger vasoconstriction reactivity to pain than non-SCD.

Maha Khaleel  Payal Shah  M Puliyl

Khaleel et al, AJH 2017

Khaleel et al. ASH 2015

P = 0.0028

Vasoconstriction Delay Time

Reactivity to Pain
Sensitization of nociceptive spinal neurons contributes to pain in a transgenic model of sickle cell disease

Giuseppe Cataldo, Sugandha Rajput, Kalpana Gupta, Donald A. Simone

Control

Sickle

WDR

HT

Cataldo et al, Pain 2015  156:722-730
Pain Anticipation causes Vasoconstriction

Both fear or anxiety of pain as well as pain itself can cause decreased perfusion

Khaleel et al, AJH 2017
Mental Stress and Pain Anticipation cause Significant Vasoconstriction Response

Significant decrease in blood flow during each mental task

Baseline  Nback  Stroop  Pain Anticipation
(N = 35)

Mean Blood Flow ± S.E

Manuscript in preparation

Maha Khaleel  Payal Shah  Saranya Veluswamy
Hypnosis increases peripheral blood flow responsivity in SCD patients.

### Table 2.

<table>
<thead>
<tr>
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<th>Control t</th>
<th>Control p</th>
<th>Control d</th>
<th>Control t</th>
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</table>
Pain management is extraordinarily complex in SCD.

Anxiety, emotions, and pain are biochemical and physiological responses, not psychiatric disorders.

Narcotics make neuropathic pain worse.
Course of Pain Crisis

Prodromal Phase
- Emotional stress
- Cold exposure
- Numbness
- Parasthesia
- Aches
- Sense that a Crisis is coming

Initial Phase
- Onset of regional pain
- Migration of pain
- Anxiety, Fear

Established Phase
- Joint effusion
- Inflammation
- Problems with Hospital personnel
- Depression
- Temp
- WBC count
- CRP
- (Steady state values)
- Hemoglobin

Resolving Phase

Relative Pain Scale

-2 1 3 7 10

Days

After Ballas 1995
Pain Crisis evolution to neuropathic pain

Prodromal Phase
- Emotional stress
- Cold exposure
- Numbness
- Parasthesia
- Aches
- Sense that a Crisis is coming

Initial Phase
- Onset of regional pain
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Established Phase
- Joint effusion
- Inflammation
- Temp
- WBC count
- CRP
- Problems with Hospital personnel
- Depression
- (Steady state values)

Resolving Phase
- Increased opioids
- Burning sensation
- Pain all over
- Nerves firing independently of VOC damage
- suggests “Nerve Pain”

Relative Pain Scale

-2 1 3 7 10 Days

After Ballas 1995
There are several kinds of Pain

Types of pain
✓ Nociceptive
✓ Inflammatory
✓ Neuropathic

Pain perception is modulated by
✓ Previous experience
✓ Anxiety and Stress
✓ Gender
✓ Many other complex issues

Von Hehn, Neuron 2012 73: Feb 23
Previous pain experience affect current pain perception


Taddio, A et al, Lancet 1997; 349:600
Stress and Gender modify pain perception

Neuropathic pain Syndromes

- Chronic pain damages neurons and they start firing by themselves with no noxious stimulus.
- Low intensity stimuli then cause perception of intense pain.
- Results from hypersensitization to pain.
- This is an organic, not psychiatric process. This pain is very real and very severe.
- Opioids as well as emotional stressors make this worse.
Pain Amplification Syndromes

- Pain is the mechanism to sense tissue damage
- Chronic pain damages neurons and they start firing by themselves with no noxious stimulus
- Low intensity stimuli then cause perception of intense pain.

- Any painful event can start this process
- Patients describe intense pain, “burning”, “hurts all over”, “my skin is on fire”
- Narcotics do not help much. Often doses are escalated with no effect. **Narcotics hypersensitize to pain can make this pain worse.**
- Anticonvulsants (Lyrica), antidepressants, muscle relaxants, massage, acupuncture, psychotherapy, physical therapy, time.

- This is the most difficult kind of pain to treat ....
- Response to treatment occurs in days to weeks or longer, not minutes to hours as is the case with nociceptive pain.
Neuropathic pain

- Typically not very responsive to narcotics
- May respond to distraction
- Burning
- Shooting pain
- Feels like I am walking on glass
- Hurts all over
- Skin is on fire. Lightest touch is painful (allodynia)
- May be associated with diffuse swelling of a limb or region of the body.
- May be associated with erythema.
- May have signs of autonomic dysfunction such as “postural orthostatic tachycardiac syndrome (POTS)”
  - Dizziness on standing
  - Sudden onset of overwhelming feeling of sleepiness, exhaustion
Myofascial pain syndrome

• Type of neuropathic pain
• Inflammatory foci develop in characteristic spots called “tender points”
• These can result in severe pain
• These points are often involved in patients with other neuropathic pain syndromes
• Probably 80% of all people will develop some type of myofascial pain at some point
Treatment of neuropathic pain

• Non-pharmacologic approaches
  – Distraction (Art, Music Rx)
  – Exercise
  – Acupuncture
  – Physical therapy
  – Massage
  – Hypnosis

• Counseling / treatment of depression, anxiety and stress

• Vocational rehabilitation
  – Get the patient back to work (school), don’t wait for the pain to go first
  – Return to normal activity will make the pain go away

• Good sleep practices

_The hospital is the worst place to be for treatment of neuropathic pain_
Drug treatment of neuropathic pain

• Anticonvulsants, in particular gabapentin (Neurontin) and pregabalin (Lyrica)
  – Increase dose to maximum over a couple of weeks
  – Should see effect within 6 to 8 weeks
• Tricyclic antidepressants and serotonin-noradrenalin reuptake inhibitors (Amitriptyline, nortriptyline, duloxetine (Cymbalta))
• Topical Lidocaine patches
• Opioids (second line Rx)
  – Methadone
  – Other opioids
  – Remember: Opioids can induce pain sensitization. The goal should be to avoid them. The pain may improve with stopping these agents.
• New agents

Even in the best of hands with full access to a multidisciplinary pain services, there is only a 40% success rate with getting rid of chronic neuropathic pain. It is a chronic disease that needs long term management.
Pain management in SCD

- Patient with SCD and with chronic pain may not show the standard physiological responses to pain (hypertension, tachycardia etc).
- Pain is one of the most difficult things to manage because we have no way to assess the severity except by the patients words.
- Never tell a patient in pain you “can tell he is not in pain”. This is about the most stupid mistake you can make. You have absolutely no way to tell for sure and telling a patient this will prove to the patient you don’t know what you are doing.
- Listen to the patient and earn their trust.
- Use adequate doses of pain meds to rapidly control VOC pain.
- Make a correct pain diagnosis and find the cause of the pain. These are complex patients with many simultaneous pathologies. Learn to recognize and treat neuropathic pain.
- Teach your families from an early age that there is a secondary type of pain “nerve pain” that is made worse by narcotics and encourage non-pharmacologic approaches to pain management.
Recap of the important stuff:

Cold, stress, anxiety and pain itself can trigger crisis. Anxiety, stress, lack of sleep make any kind of pain much worse.

It is very important to get control of severe "crisis" pain with adequate doses of pain medications quickly (but)
Narcotics make you more likely to get neuropathic pain and make neuropathic pain worse.

SCD patients can have both kinds of pain at the same time
Patients and medical providers need to know the difference between pain from tissue damage (VOC) and neuropathic pain. They also need to know the differences in management strategy.
Quaerite Veritatem:

Seek the Truth

(And stay as far away as possible from those who think they have found it ...)

Thank you for your attention
Executive Summary

- All SCD pathology is explained by the relation between delay time (give HU to increase delay time) to polymerization and rate of microvascular flow (hydrate, keep warm, anti-inflammatory, anti-adhesive, anti-stress to increase flow).
- Fear, anxiety, pain cause significant vasoconstriction and probably promote Vaso-occlusion. They also markedly increase perception/severity of any type of pain.
- **Recognition of neuropathic pain is critical.** It does not respond well to narcotics. Narcotics hypersensitize patients to pain and make neuropathic pain worse.
- All patients with SS and S-B\(^0\)thal should be on maximal doses of HU starting at 9 mo of age regardless of crisis frequency. L-Glutamine in addition may be helpful.
- All patients with SS and S-B\(^0\)thal with HLA matched sibs or >10/10 MUD matches should be encouraged consider BMT.