Sickle Cell Disease
New Treatment Options for Patients (FINALLY!)

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Speaker Disclosure Statement

Robin Pitts, C-FNP, MN, BSN, CPHON has no industry relationships to disclose
Objectives

• Encourage session attendees to view caring for sickle cell patients as
  – COMPELLING
  – CHALLENGING
  – REWARDING

• Review historical significance of sickle cell disease

• Discuss pathophysiology of pain in sickle cell disease

• Discuss established and new treatment options

• Where do we go from here?
History

• 1910 - Dr. Herrick and Dr. Irons, Chicago IL
  – First to note “odd shaped red blood cells that looked like a sickle” in a patient with pneumonia

• 1922 – John Hopkins Hospital
  – First noted use of the term “sickle cell anaemia”

• 1933 – Memphis TN
  – Terms “latent” and “active” were used to describe the disease
  – Clarified as heterozygous and homozygous inheritance that same year by a geneticist in Ann Arbor MI
History

• 1954
  – Hemoglobin electrophoresis widely available

• 1960’s
  – The Black Panther Party championed and pushed for implementation of a national sickle cell screening program along with establishing grass roots health clinics to serve primarily Black and impoverished communities

• 1972
  – Sickle Cell Anemia Control Act passed by Congress
    • “Sickle cell anemia is a debilitating inheritable disease that afflicts approximately 2 million American citizens and has been largely neglected”
History

• 1986 - PROPS study
  – Studied efficacy of Penicillin prophylaxis in infancy for those with sickle cell disease in decreasing incidence of life threatening pneumococcal infection

• 1987 - NIH Consensus Conference
  – Recommendation for universal newborn screening for sickle cell disease

• 2006 – ALMOST 20 YEARS LATER
  – All states require and provide universal newborn screening for sickle cell disease
  – Mortality has decreased by 50% in ages 1-4yo
Sickle Cell Overview

- Autosomal recessive disease

- Valine is found in place of glutamic acid on the beta chain of the hemoglobin (Hgb) molecule

- This defect causes the cell to polymerize or “sickle” when oxygen is released

- Sickled cells have increased adhesive properties and bind with platelets and leukocytes

- Life span of erythrocyte is decreased significantly

- Cell death leads to chronic hemolytic anemia
Statistics

• Over 100,000 people in the United States are affected by sickle cell disease

• Average life expectancy is 40-45 years old

• Average cost over a lifetime $1 million/patient

• Approximately 75% of hospital admissions start with an ED visit (*where they may or may not have seen a hematologist or been treated with a standard of care for sickle cell pain)

• Sickle cell patients (on average) wait 25% longer than general patients to be seen in a hospital emergency room
Pain Sickle Cell Disease

- Pain is known as the hallmark of sickle cell disease

- Genotypes most likely to experience pain
  - Hgb SS
  - Hgb SC
  - Hgb Sbeta (0/+ ) thal
Pain Triggers

- Extreme temperature changes
- Dehydration
- Change in barometric pressure
- Stress
- Fatigue
- Overexertion
- Unknown etiologies
“10 Redefined” artist Hertz Nazaire
Pain
Patient Description

• Feels like I am drowning in the pain.

• Feels like a toothache all over, magnified 100 times

• Feels like a migraine headache, except that it affects my whole body

• Sickle cell pain is enveloping, you can do nothing about it. It controls you, you have no control over it
Pain
Medical Definition

• An unpleasant sensation that can range from mild, localized discomfort to agony.

• Has both physical and emotional components.

• The physical part of pain results from nerve stimulation.

• Is mediated by specific nerve fibers that carry the pain impulses to the brain where “their conscious appreciation can be modified by many factors”
Pain
Influencing factors

• Developmental stage
  – Ability to self regulate and cope with discomfort

• Previous pain experiences

• Precipitating events

• Gender

• Family and sociocultural factors

• Inflammation

• Chronic opioid use
Pain Considerations

- Subjective
- Highly personal
- Unique
- Almost impossible to measure or quantify clinically
Someday we will understand how the same virus can cause a runny nose in women and a life threatening man flu in men...
Pain
Sickle Cell Disease

• The medical definition of CHRONIC pain is very inadequate

• Clearly patients with sickle cell disease can have several different types of pain including concurrent acute and chronic pain

• Multiple factors in sickle cell disease contribute to chronic pain over time
  – Vessel wall damage
  – Chronic inflammation with increased inflammatory markers
  – Central nervous system sensitization
"Wow. That Tylenol really took away my pain." said no one ever.
Sickle Cell Pain Components

- Micro-vascular obstruction (vaso-occlusion)
- Decreased oxygen supply to tissues
- Cellular adhesion
- Cell death
- Inflammation
- All these lead to a “noxious micro-environment” which can trigger peripheral and central pain pathways
Noxious micro-environment

- Chemical mediators released following tissue damage and inflammation
  - Cytokines
  - Growth factors
  - Tryptase
  - Substance P
  - Amines

- These inflammatory mediators directly activate nerve endings which evoke the initial pain response

- When in constant production the nerve endings are constantly being impacted
Noxious micro-environment

• Endothelin-1 levels elevated
  – Potent, long acting amino acid peptide
  – Mediator of vaso-constriction and inflammation
  – Increased production with hypoxemia

• PGE2 levels elevated
  – Potent inflammatory mediator
  – Sensitizes nociceptors
  – Induces hyperalgesia

• Tryptase, Substance P and P-selectin
  – Activation of mast cells
  – Mediators of chronic inflammation
  – Urticaria
  – Neuropathic pain
Noxious micro-environment

- Blood vessel obstruction leading to tissue ischemia
  - Vaso-occlusion

- Cellular adhesion
  - Platelets, lymphocytes

- Release of cytokines with cell death
  - Substance P, P-selectin
  - Endothelin-1
  - Mast cell activation

- Chronic inflammation
  - Vessel wall irritation and narrowing
What Doesn’t Kill You Makes You Stronger (?)
What doesn’t kill you makes you stronger

Stand a little taller

Doesn’t mean I’m lonely when I’m alone

What doesn’t kill you makes a fighter

Footsteps even lighter
Conceptualization

Hemolysis

Hgb S polymerization

VOC

Pro: inflammatory thrombotic

Nitric Oxide decreases

SILENT SYSTEMIC VASCULOPATHY

Endothelial dysfunction

Leukocyte & platelet adhesion
Hydroxyurea

• Chemotherapeutic agent - antimetabolite

• Mechanism of action
  – Increases fetal hemoglobin production
  – Increases size, oxygen carrying capacity and life span of erythrocyte
  – Decreases expression of erythrocyte adhesion receptors

• Side effects
  – cytopenias, decreased sperm count, teratogen
Hydroxyurea

• FDA approved in 1998 for the treatment of adults with sickle cell disease.

• Available products
  – Droxia 200mg, 300mg, 400mg, Hydrea 500mg
  – Siklos 100mg (non-scored tabs), 1000mg (scored)
  – Liquid suspension

• Cost
  – Approx $1000/year

• Outcomes
  – Decreased incidence of VOC, increased hemoglobin levels
Pre Hydroxyurea
Post Hydroxyurea
New(er) Treatment Considerations

• Vitamin D
• Glutamine
• Voxelotor
• Crizanlizumab
Vitamin D

• Fat soluble vitamin, critical for bone growth

• Mechanism of action
  – Significant anti-inflammatory action

• Sources
  – Fortified dairy products (milk, yogurt, cheese) and breakfast cereals
  – Fatty fish, beef liver, egg yolks
  – Sunlight

• Vitamin D3 supplement – cholecalciferol
  – Chemically similar to what is found naturally in the body
Glutamine

• L-glutamine is an essential amino acid

• Sickled cells are in a constant state of oxidative stress/imbalance

• **Mechanism of action**
  • Increased availability of L-glutamine for use by stressed erythrocytes
  • Decreased erythrocyte adhesion
  • Reduces oxidative damage in red blood cells (RBC), increasing their flexibility and ability to transport oxygen

• **Side effects**
  — nausea, fatigue, non-cardiac chest pain, back pain
Glutamine

- FDA approved for ages 5 and older in 2017
- Once daily, tablet
- Cost
  - $24-50K/year
- Outcomes
  - Median number of pain crises was 25% lower with L-glutamine vs placebo
  - Decreased hospitalizations by 33%
  - Significantly lower numbers of acute chest syndrome with L-glutamine vs placebo
Voxelotor

• Polymerization inhibitor

• Mechanism of action
  – Binds to hemoglobin to increase oxygen affinity of erythrocytes
  – Normal erythrocyte function and oxygen delivery is restored

• Side effects
  – headache, diarrhea, abdominal pain, fatigue
Voxelotor

- Fast tracked FDA approval for ages 12 and older in 2019

- Once a day, tablets (500mg each)

- Cost
  - $80-120K/year

- Outcomes
  - 65% of patient receiving 1500mg dosing achieved >1g/dl increase in hemoglobin
  - Within 2 weeks, hemoglobin level increased by approx 40% from baseline
Crizanlizumab

- **Anti P-selectin monoclonal antibody**

- **Mechanism of action**
  - Binds to and blocks P-selectin
  - Reduces the ability of erythrocytes to stick to other cells (mainly platelets and leukocytes)
  - Reduces inflammation and stickiness of the endothelial wall
  - Decreases vessel wall irritation

- **Side effects**
  - arthralgias, back pain, nausea, pyrexia
Crizanlizumab

- Approved by FDA for ages 16 and older in 2019

- Monthly, IV infusion over 30 minutes

- Cost
  - $80-125K/year

- Outcomes
  - 50% of participants on highest dose had no crisis vs placebo group
  - Annual rate of days hospitalized 4 vs 6.87
  - Delayed onset of first and second VOC
Now What?
Chronic Pain

• 30% of adults with sickle cell disease report daily pain

• 50% have enough symptoms to meet the diagnosis of chronic pain
“Chronic sickle pain may be a distinct pathophysiologic entity because the initial origin of injury may not be relevant once sensory pathways shift to a state of hyperexcitability”

Tran, 2017
Chronic Pain

• Mechanism of pain in sickle cell disease remains poorly understood

• Traditionally defined as pain lasting longer than 3 months
  – Damaged neurons continually send impulses in absence of stimulus
  – Intense pain can be perceived with low intensity stimuli
  – Hypersensitive reaction to pain
  – Real physical pain – not primarily a psychological or psychiatric situation

• An acquired nervous system disorder

• Involves pathological alterations at all levels of the nervous system
Chronic Pain

• The most common cause of emergency room visits and hospital admissions for patients with sickle cell disease is VOC pain

• Total medical costs exceed $1.1 billion annually

• Minority patients are at greater risk for perceived discrimination and under-treatment of their pain which contributes to:
  – Greater clinical pain severity
  – Decreased coping strategy
  – Greater psychological impact of pain
  – Decreased trust in medical providers
Non-pharmacologic Treatment

- Music
- Art
- Child life
- Exercise
- Acupuncture
- Heat and Massage
- Physical therapy
- Hypnosis/Biofeedback
- Psychology/Counseling support
- Activities of Daily Living – school, work, sleep hygiene, diet
Pharmacologic Treatment

• Hydration
• Non-steroidal medications (NSAIDS) – ketorolac, ibuprofen
• Topical patches – lidocaine 5%
• NSAID lotions/creams – diclofenac
• Anticonvulsants – pregabalin, gabapentin
  – turn down sensitivity of damaged nerve fibers
  – decrease pain signals sent out by damaged nerve fibers
• Tricyclic Antidepressants - amitriptyline, nortriptyline
  – increase neurotransmitters in spinal cord that reduce pain signals
• Opioids - second line therapy
  – approximately 25% of patients prescribed opioids for chronic pain misuse them
  – approximately 10% will develop an opioid use disorder
Thoughts

• Once the damage is done it is very difficult to undo – both physically and psychologically

• Providers and caregivers must learn how to be PROACTIVE vs REACTIVE

• Use all the tools in the pain toolbox
  – Non-pharmacologic interventions
  – Pharmacologic interventions
Final Thoughts

“The lack of research funding, attention, and treatment of sickle cell are considered a matter of racial inequity. It is a **Black Lives Matter** issue because it is primarily a genetic disease that affects Black people who often also have fewer financial resources.”

W. Bloom, 2019