Native South Carolinians’ Rare (Or not so Rare) Diagnosis

Joseph A. DeStefano, MD F.A.C.P

Case 1

- **CC:** “My memory is bad, I am disabled from depression"
- **HPI:**
  - 50 yr old white male, retired attorney who presents for complete Physical with above chief complaint. Patient was practicing law until he started having memory problems and was afraid he would forget to show up for court. He complained of fatigue, decreased Libido, Joint aches, and bad temper.
  - Had been to Emory and saw a psychiatrist on a regular basis in Atlanta. Came in looking for a diagnosis

- **PMH:** Depression, OSA
  - wears CPAP
- **PSH:** Negative
- **Soc HX:** Disabled (retired) Attorney No smoking occasional Alcohol
- **ROS:**
  - Depression, Poor Memory, dyscoordination, arthritis pain in hands wrist ankles, decreased libido
  - **FamHX:** Father d/c 60 he was wheelchair bound and lost use of legs in end never given a diagnosis what he died of Mother Alive in 80’s Dementia and debility and CHF
  - CPE
  - AF/VSS

- **Normal exam except some dark spots on skin of ankles and elbows, very tan w/o tan lines
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- **Asked if he was of American Indian descent. He said no, everyone was white SC since revolution. Scotts-Irish and English descent
- **CMP:** Normal minimal elevation AST
- **B12 and Folate:** Normal
- **TSH/T4:** Normal
- **Testosterone:** 150
- **CBC:** Pretty normal slight increase in HCT

- **What other labs needed?**
  - **What is the suspected Diagnosis?**

**Assessment**

- Depression
- OSA
- Decreased Libido
- Arthritis

Case Study 2

- **CC:** “I can’t get out of bed”
- **HPI:** 77 yr old Female originally from Rockhill SC who called her daughter who lived 8 hours away and asked her to come get her because she could not get out of bed. Patient presented to the Medical Admission Center of Memorial Hospital in Chattanooga. Patient displayed some hypo-manic behavior With micrographia. She was not able to transfer out of bed without assistance despite 5/5 motor in all extremities’. She had Anasarca with 2-3 + edema in bilateral lower extremities

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- **CMP:** Normal minimal elevation AST
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- **Testosterone:** 150
- **CBC:** Pretty normal slight increase in HCT

- **What other labs needed?**
  - **What is the suspected Diagnosis?**
**HPI:** Patient stated that she had been in decline and had been in and out of multiple hospitals in the Rockhill and Charlotte area. Her problems included recurrent falls, including one bad incident where she fell in front of her mailbox on a fire-ant pile and could not get up. She was found by neighbors and sent to hospital via ambulance. She also complained of shaking spells and weakness. She had poorly controlled diabetes. She was just sent home from local ER before she called her daughter to come get her. Her daughter was surprised because the patient had been paranoid, and refused all previous offers of help.

**PMH:** Diabetes, HTN, Arthritis, Frequent Falls
Several hospitalizations for falls and confusion, Chronic Herpetic neuralgia with CPS and Doctor shopping
An extremely prolonged hospitalization about 3 years before for: UTI, HHNS, Sepsis and Thrombocytopenia after a steroid epidural injection for pain

**PSurgH:** Cholecystectomy, TAH/BSO

**OBHX:** 2 Pregnancies 13 years apart multiple miscarriages between

**Soc:** Widowed, no smoking ETOH in distant past non-smokers Retired CNA

**ROS:** Episodic confusion, shaking, and frequent falls, arthritis pain in hands, wrists, elbows, knees, and ankles. Chronic herpetic neuralgia, uncontrolled diabetes and hx Hypothyroid. Easy bruising, and free bleeding, mild DOE, swelling and rash LE. Depression, hypomania, paranoia, and rage attacks. No Nausea, Vomiting or occasional bouts of Diarrhea.

**FHx:** Both parents DC. Hands, wrists, elbows, knees and ankles. Chronic herpetic neuralgia, uncontrolled diabetes and hx Hypothyroid. Easy bruising, and free bleeding, mild DOE.

**PE:** Disheveled, appearing elderly, white female who appeared older than stated age. Hypomania with pressured speech, Heent ATNC EOMI, PERLA. No Facial drop or asymmetry

**Lungs:** Slight crackles at bases

**CXR:** Mild vascular congestion

**Extremeties:** 1+ edema in arms and hands, 2+ in legs, Red cellulitic Rash to bilateral knees

**UA:** No infection

**CBC:** WBC 15K H/H 12/36 Plt 70's

**CMP:** Mild elevated transaminases 70's

**BS:** 300

**Echo:** Ef 50's mild DD

**CXR:** Mild vascular congestion

**What additional labs or imaging do you need? Which one has the money?**

**Assessment**

1) Debility and frequent Falls
2) Uncontrolled DM
3) HTNHD with DD
4) Herpetic Neuralgia with CPS-Opiate dependent
5) Cellulitis
6) Mild abnormal Transaminase
7) Thrombocytopenia
8) Bipolar Spectrum disorder hypomanic phase with hypermicrographia
2 Cases 1 Diagnosis

• What is the major unifying diagnosis in both cases?

Occam’s Razor
lex parsimoniae

• The principle (attributed to William of Occam) that in explaining a thing, no more assumptions should be made than are necessary.
• Medical Application: Diagnostic parsimony
  – Diagnostic parsimony advocates that when diagnosing a given injury, ailment, illness, or disease a doctor should strive to look for the fewest possible causes that will account for all the symptoms.

Case 1: The Money Labs

• Iron sat: 45%
• Hepatic Iron Index: 2.5 on US guided liver biopsy but No Cirrhosis on Biopsy
• Genotype: 282 homozygote

Case 2: The Money Labs

• Ammonia: 110
  – thus Hepatic encephalopathy causing shaking spells and lack of coordination
• Iron Sat: 85%
• Hep Iron Index: 2.1 on Biopsy, Cirrhosis on Biopsy
• Genotype: 282 homozygote

Hereditary Hemochromatosis

Joseph A. DeStefano, MD F.A.C.P

Hereditary Hemochromatosis

What is it?

• Genetic disorder of iron metabolism, causing an excess amount of iron to be absorbed
• a.k.a. Haemochromatosis, HHC, or ’The most common preventable disease you rarely hear about’
Hereditary Hemochromatosis

**HHC is Under Recognized and Under Treated**

- Approximately 1 in 10 (US) carry trait
- Overall carrier frequency (SC)
  - C282Y: 1/11 (All Races)
  - H63D: 1/7 (Caucasians)
- Approximately 1 in 250 Americans have HHC; about 1-1.5 million affected
- HHC incidence: > 10 times C.F. and P.K.U. deficiency combined

Iron Metabolism

**A Little Is Good, More Is Not Necessarily Better**

- Iron is important in multiple processes, including RBC production, muscle and enzyme function
- Normally, iron is absorbed in a controlled fashion through the intestines
- Normal requirements = normal absorption; Approximately one milligram/day

Iron Metabolism

**Iron Transport and Storage Proteins**

- Absorbed iron transported through the bloodstream by Transferrin
- Iron stored by cells in combination with Ferritin or Hemosiderin

Iron Metabolism

**Multiple Causes of Iron Overload**

- Transfusions
- Dietary, includes vitamins / health foods
- Alcohol
- Blood diseases (various, rare)

Iron Metabolism

**Excess Iron Is Toxic to Multiple Organ Systems, Including**

- Liver
- Heart
- Pancreas
- Joints
- Pituitary gland
**Inheritance**

*Autosomal Recessive*

- Two germline mutations (one from each parent) are required to develop disease; equally transmitted by men and women.
- 25% risk to each offspring of a couple who are both carriers.

**Mutations**

- C282Y
- H63D
- Heterozygote: one mutation
- Homozygote: two of same mutation
- Compound Heterozygote: one each C282Y/H63D

**Sibs**

*Risk CAN be up to 50%*

- Usually the risk of having HHC for sibs of a proband is 25%.
- The high carrier frequency in the general population of European origin (1/9, or 11%) means that, on occasion, one parent has two abnormal HFE genes (usually in the absence of clinical findings).
- In such instances, the risk for sibs to have two mutations is 50%.

**Incomplete Penetrance**

*An Important Concept in Pedigree Analysis*

- Incomplete penetrance
  - Person has the mutant gene(s) but no clinical symptoms.
- A large, but yet undefined, fraction of homozygotes and compound heterozygotes for HHC do not develop clinical symptoms.
- Currently, no tests are able to identify those individuals who are likely to develop symptoms and morbidity.

**Hereditary Hemochromatosis**

*Signs and Symptoms*

- Classical presentation of “Bronze Diabetes” is uncommon.
- Signs and symptoms depend on extent and duration of iron accumulation.

**Hemochromatosis**

*Early Signs and Symptoms*

- Fatigue
- Palpitations
- Joint pain
- Abdominal / stomach pain
- Impotence
- Liver enzyme abnormalities
- Severe infections from Vibrio, Salmonella
Hemochromatosis
Later Signs and Symptoms

- Gray or bronze skin pigmentation
- Liver disease: esp. cirrhosis and hepatoma
- Heart disease, esp. congestive heart failure and arrhythmias
- Diabetes: esp. adult onset insulin dependent
- Multiple endocrine abnormalities, including hypothyroidism, hypogonadism, Addison’s

Hemochromatosis
Treatment

HHC Is a “Preventable” Disease

- Early detection and treatment can prevent essentially all complications of hemochromatosis
- Treatment is directed towards removing excess iron from the body

Hemochromatosis
Detection

HHC Is a “Preventable” Disease

Suspect HHC in patient with:

- Fasting transferrin-iron saturation percentage (Tsat%) >45%
- Serum ferritin >250ng/mL
- Confirm with genetic test

Hemochromatosis
Treatment

Phlebotomy (blood donation): each unit removes ~250mgs of iron

Frequency depends on levels: serum ferritin, TS% & patient’s health

Hemochromatosis
Monitoring of Therapy

Indicators:

- Ferritin 25-75 ng/mL
- Transferrin saturation 25-35%
- MCV decreases ~3%

Monitoring of Therapy

- Follow laboratory parameters; treat until evidence of iron overload absent
Hemochromatosis Treatment Options

_HHC Is a “Preventable” Disease_

- **DRC**: limited availability
- **Chest port**: invasive procedure
- **Chelation**: less commonly used; reserved for pts unable to donate blood

Hemochromatosis Treatment Adjunct

_HHC Is a “Preventable” Disease_

- Dietary modifications
- Limitation of alcohol
- Avoidance of iron & Vitamin C supplements
- Avoidance of uncooked shellfish

Hemochromatosis Case Report

**Mr. A.N., 32 y.o. male**

- **Patient**: “get acquainted” visit
- **Chief complaint**: fatigue
- **P.M.H.**: appendectomy, age 14
- **F.H.**: positive for diabetes
- **Soc. Hx.**: no smoking, occasional alcohol
- **P.E.**: no significant findings

Hemochromatosis Case Report

**Mr. A.N., 32 y.o. male**

- **Laboratory evaluation**
  - **T.S.H.**: normal
  - **HgbA1c**: normal
  - **C.B.C.**: normal
  - **A.L.T.**: slightly elevated at 57

Hemochromatosis Case Report

**Mr. A.N., 32 y.o. male**

- **Laboratory evaluation**
  - **Hepatitis profile**: negative
  - **Microsomal antibody assay**: negative
  - **A-1 Antitrypsin level**: normal
  - **Iron saturation %**: 86%
  - **Ferritin**: 1440

Hemochromatosis Case Report

**Mr. A.N., 32 y.o. male**

- **Laboratory evaluation**
  - **Hemochromatosis gene assay**: positive: 1 copy of Cys282Tyr, 1 copy of His63Asp
  - **C.T. abdomen**: normal
**Hemochromatosis**

*Case Report*

**Mr. A.N., 32 y.o. male**

**Treatment plan**

| Pt. Referral | Therapeutic phlebotomy on weekly basis |
| Monitor      | Serial H/H, Ferritin levels |
| Family referral | Genetic counseling |
| Prognosis    | Excellent |

**Hemochromatosis**

*Management: Challenges*

**Underbleeding**

- Some patients need two phlebotomies per week; DRCA
- Serum ferritin <1,000ng/mL < 1% chance of fibrosis

**Overbleeding**

- De-iron without iron deficiency: Evidence supports: maintaining a pre-phlebotomy Hgb 12.5g/dL and Sf >55%
- Body responds to overbleeding by increasing iron absorption
- Patient becomes iron avid

**Little or no genetic info or counseling**

- Patient often confused by genetic results
- Opportunity to diagnose and begin treatment early in blood relatives

**Few or no diet recommendations**

- Besides the name of a qualified physician, diet info is the #1 request made by patients

**To Sum Up Hemochromatosis**

- The most common genetic Ds in U.S.
- Involves excess iron absorption and toxicity
- Under-recognized as cause of diabetes, endocrine disorders, cirrhosis, arthropathy, and Ca
To Sum Up  
Hemochromatosis

• Can be identified with existing technology
• Treatment is safe & effective, prevents complications, and benefits blood supply
• IDI recommends screening

Hemochromatosis  
Resources

OSU Hemochromatosis Program
Mark Wurster
614-293-2281
wurster-1@medctr.osu.edu

Centers for Disease Control
www.cdc.gov/hemochromatosis/training/index.htm

Hemochromatosis  
Resources

National Society of Genetic Counselors
http://www.nsgc.org
Iron Disorders Institute
PO Box 675, Taylor SC, 29687
Ph: 888-565-4766
info@irondisorders.org
www.irondisorders.org
www.hemochromatosis.org

HHC Gene Frequencies in South Carolina

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Info Courtesy of: John W. Longshore, Ph.D., FACMG
Molecular Diagnostic Laboratory
Greenwood Genetic Center

Hereditary  
Hemochromatosis

• Autosomal recessive disorder on 6p
• Leads to progressive iron overload of organs and tissues
• Initial symptoms
  - weakness
  - weight loss
  - joint pain
• Long term effects
  - cirrhosis
  - diabetes mellitus
  - hepatic carcinomas
  - cardiac complications

Powell, Harrison’s Principles of Internal Medicine
Diagnosis of Hemochromatosis

- Traditionally diagnosis was made via liver biopsy and iron staining.
- Serum ferritin and transferrin saturation levels are quite helpful.
- DNA testing allows rapid diagnosis, is more accurate than liver biopsy, and cost effective.
- Two primary and one minor gene defects:
  - C282Y
  - H63D
  - S65C
  - Treatment via phlebotomy.

Study Population

- 1376 consecutive births from Self Memorial Hospital in Greenwood, SC
- 51% male and 49% female
- 55.0% Caucasian
- 40.0% African-American
- 3.0% Hispanic
- 2.0% other or not reported

Genotypes for Hereditary Hemochromatosis

- C282Y Data
  - Caucasian (n=765)
    - Homozygotes 0.78%
    - Heterozygotes 13.86%
    - Normal 85.36%
  - African-American (n=536)
    - Homozygotes 0.19%
    - Heterozygotes 2.05%
    - Normal 97.76%
  - Hispanic (n=41)
    - Homozygotes 0.0%
    - Heterozygotes 7.32%
    - Normal 92.68%

- H63D Data
  - Caucasian (n=765)
    - Homozygotes 2.88%
    - Heterozygotes 24.97%
    - Normal 72.16%
  - African-American (n=536)
    - Homozygotes 0.19%
    - Heterozygotes 5.60%
    - Normal 94.22%
  - Hispanic (n=41)
    - Homozygotes 2.44%
    - Heterozygotes 21.95%
    - Normal 75.61%

- C282Y/H63D Compound Heterozygotes
  - Caucasian (n=765)
    - 2.75% C282Y/H63D
  - African-American (n=536)
    - 0.19% C282Y/H63D
**HHC Allele Frequencies**

<table>
<thead>
<tr>
<th>Race</th>
<th>C282Y</th>
<th>H63D</th>
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<tbody>
<tr>
<td>Overall</td>
<td>5.02%</td>
<td>10.39%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>7.71%</td>
<td>15.36%</td>
</tr>
<tr>
<td>African-American</td>
<td>1.21%</td>
<td>2.99%</td>
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**South Carolina Screening Data Conclusions**

<table>
<thead>
<tr>
<th>Overall carrier frequency</th>
<th>C282Y</th>
<th>H63D</th>
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<tbody>
<tr>
<td>European/African-American admixture</td>
<td>18.89%</td>
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<tr>
<td>Both C282Y and H63D mutations were found in every race studied</td>
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<tr>
<td>C282Y allele frequency in SC Caucasians is statistically significant when compared to other published prevalence studies</td>
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**Why is Counseling Important for HHC Testing?**

- Explanation of positive and negative test results and how they are to be interpreted
- Accurate pedigree and family history
- Understand the inheritance of HH and who is at risk given prior family testing results
- Insure informed consent is obtained
- Counselors have specialized training for communicating test results to individuals and families
- Nonpaternity

**Nonpaternity: a huge issue**

- Recent example at GGC
  - 66 year old male was referred due to elevated iron studies and genotyping showed him homozygous for C282Y
  - His 28 year old daughter was subsequently referred for genetic counseling and hemochromatosis testing. Her genotype was normal

**Nonpaternity: a huge issue**

- Both father and daughter were retested 3x with the same results and sequence analysis was utilized which confirmed the earlier results
- The daughter approached her mother about the results and her mother denied any chance of nonpaternity
- Microsatellite analysis was utilized to confirm the nonpaternity at the daughter’s request

**Heterozygote Advantage**

- Why are HHC genotypes so frequent in the general population?
- Hemochromatosis heterozygotes have a protective advantage against anemia
- Why are HHC genotypes so frequent in South Carolina Caucasians?
  - Irish, Scots-Irish, and English Ancestry
Why is this Data Significant?

- HHC is very frequent in the general population and represent a major opportunity for the convergence of primary care medicine and genetics
- Most primary care physicians see patients with HHC every week and most go undiagnosed
- Morbidity and mortality associated with HHC is largely preventable with early diagnosis and treatment

Conclusions

- HHC risk factors were found in all races studied and co-inheritance of multiple risk factors is not as rare as expected
- HHC is an extremely common genetic disorder in our area
- DNA testing for HHC should be accompanied by serum ferritin and transferrin saturation assays to resolve inconclusive genotypes

Conclusions

- In hemochromatosis, at risk family members should be studied before overload begins to prevent morbidity and mortality from excess iron
- DNA testing allows rapid and accurate diagnosis for these common conditions