Hereditary Hemochromatosis: Dispelling the Myths

Carlyn Volume-Smith, B.Sc.Pharm., M.Sc., Ph.D.
Conflict of Interest Declaration

Carlyn Volume-Smith, B.Sc.Pharm.M.Sc.,Ph.D.

I have no conflicts to declare
Agenda

- Learning objectives
- To develop and understanding/awareness of:
  - what hereditary hemochromatosis is
  - how one inherits hereditary hemochromatosis & who it typically affects
  - what iron overload is and what is consequences are
  - how hereditary hemochromatosis is diagnosed
  - how iron overload is treated
  - how pharmacists can support patients with hereditary hemochromatosis
Myth 1:
Hereditary Hemochromatosis is really rare
What is it?

- Hereditary hemochromatosis (HHC) is a genetic, metabolic disorder that results in iron overload
  - It is the most common genetic disorder in the western world, affecting an estimated 1 in 300 Canadians.
  - In individuals of Northern European descent, the prevalence as high as 1 in 227
    - Ireland and France have the highest prevalence of the disorder
    - French, English, Welsh, Irish, Scottish
- Also called “Celtic Curse” or “Bronze Diabetes”
A genetics refresher

- HHC is an autosomal recessive disorder - estimated that about 10% of the Caucasian population are carriers.
- Classic HHC is caused by mutations of the $HFE$ gene.
- Mutations of the $HFE$ gene result in low levels of functional hepcidin - a protein that regulated iron absorption in the body- which in turn leads to excess absorption of iron in the gastrointestinal tract.
So what if there is extra iron absorption?

- Normally - The body has about 4,000 mg (4 grams) of iron
  - ~3,000 mg is contained in hemoglobin
  - ~500 mg is bound to the storage protein ferritin
  - ~300 mg is stored in the liver.

- With HHC
  - The gut absorbs iron at 2-4 times the normal rate, despite the body already being overloaded with iron.
  - The level of ferritin increases to try to contain excess iron.
  - A person suffering from iron overload typically can have 15-60 grams of iron upon diagnosis.
Where does all this excess iron go?

Liver

Pancreas

Heart

Endocrine glands

Joints
Myth 2:
Hereditary hemochromatosis is readily identifiable and easy to diagnose
How does a typical patient with iron overload due to HHC present?

- Mr. P.
- 33-year old male
- Physician refers him to purchase a splint for his wrist(s); complaining of joint pain in thumbs and index finger.
- Mr. P. mentions he might want to purchase medication for pain as well.
- Medication profile indicates that he is a healthy male, no allergies.
- Has had three antibiotics prescribed over the last 10 years; nothing in the last two years.
- You provide him with the required splint and advise that he can take acetaminophen as directed, as needed.
Who does it usually affect?

- Primarily people of Northern European descent
- Too often, diagnosis does not come until signs or symptoms become severe
- In men, accumulation of iron generally does not begin presenting itself until late 20s or early 30s
- Women, naturally protected by menstruation, may not show effects until about 10-15 years after they stop having a period due to menopause, birth control pills or hysterectomy (*BUT NOT ALWAYS*)
- Diagnosis of one individual *should* lead to additional diagnosis within the immediate family
Another interaction with Mr. P.

- Mr. P. and his wife come in looking for OTC vitamins.
- Mr. P.’s Wife is looking for pre-natal vitamins and while you are helping her select some, he mentions that he has been feeling tired in the last little while
- He is looking for iron supplements specifically
- You re-acquaint yourself with his profile and ask some additional questions.
- Refer him to his primary care physician
Signs and Symptoms

- Symptoms often attributed to other causes
- Symptoms of HHC do not necessarily appear in a particular order, and importantly, not all hemochromatosis sufferers will have every symptom
  - Arthritis, especially in their hands, in particular, knuckles of first and second finger and thumb
  - Chronic fatigue
  - Loss of sex drive (libido) or impotence
  - Amenorrhea
  - Abdominal pain
  - High blood sugar levels
  - Hypothyroidism
  - Abnormal liver function tests, even if no other symptoms are present
Iron-related Proteins

- **Serum Ferritin (SF)**
  - protein that stores unused iron
  - acute phase reactant
  - Normal Men: 50-300 ng/mL; women 20-250 ng/mL
    - Elevated 300-999 ng/mL
    - Abnormal >1000 ng/mL

- **Transferrin Saturation (TS)**
  - protein that carries iron between organs, transfers iron to cells and bone marrow
  - 25-40% is normal; >45% saturation is high
Genetic Testing

- Genetic testing is definitive -
- The HFE gene has three known mutations which cause hemochromatosis
  - C282Y mutation (most common)
  - H63D mutation
  - S65C mutation.
- Genetic counselling is a good idea
- ALL FIRST-DEGREE RELATIVES of individuals who have a clinical diagnosis of hereditary hemochromatosis would benefit from having a genetic test
Myth 3:
Hereditary Hemochromatosis isn’t a big deal
What are the long-term complications of HHC

- It depends.....

- Assessment of potential end-organ damage
  - For example - The liver:
    - Liver enzymes
    - Radiological imaging of liver (MRI)
      - primary liver cancer (hepatoma), a complication that occurs in about 25% of patients with cirrhosis resulting from HHC.
Six months later - Mr. P. visits the pharmacy

- Insurance blood work showed elevated liver enzymes - denied coverage
- Family practitioner: Enlarged spleen, liver and abdominal lymph nodes; negative for Hepatitis A and B
- Referred to gastroenterologist: tested ferritin (>9000ng/mL); HHC? Leukemia?
- Referred to hematologist: confirmed HHC with genetic testing
- Additional testing occurring to assess end organ damage - echocardiogram, MRI
Myth 4: There are several efficacious medications used to treat the disorder.
How is iron overload treated?

- Gold standard is phlebotomy
  - Each unit of blood contains 225 mg of iron within hemoglobin
  - Phlebotomy once-twice a week until iron reaches 105 g/L-110 g/L.
  - Iron mobilizes out of organs and into the bone marrow for manufacturing of more red blood cells
  - Some clinicians monitor ferritin levels during de-ironing, moving to maintenance when ferritin levels drop below 50 ng/ml
Maintenance Phlebotomies

Goal:

- Transferrin saturation between 30-40% while maintaining a normal hemoglobin (normal hemoglobin range is 140-180 g/L for men and 120-160 g/L for women).

- Phlebotomy every 3-4 months; FOR LIFE

- If a person with hemochromatosis is otherwise eligible, he/she can become a regular donor at Canadian Blood Services (CBS).
Other interventions

- Limit intake:
  - Avoid taking iron, including iron pills, iron injections, or multivitamins that contain iron.
  - Limit vitamin C intake, as it enhances iron absorption
  - Avoid uncooked fish and shellfish (esp oysters and clams). Some fish and shellfish contain *Vibrio vulnificus* bacteria that can cause infections in people who have chronic diseases, such as hemochromatosis.
  - Limit alcohol intake

- Ensure vaccinations up to date
  - Especially for Hepatitis A & B
Chelating Agents

- Very rarely used
- Mechanism of action: Essentially bind metal ions so that they are water soluble and can be excreted in kidneys
  - Desferoxamine
  - Deferasirox
- NOT efficient
- Concerns regarding toxicity
Myth 5: Pharmacists don’t have a role in supporting patients with hereditary hemochromatosis
What can the pharmacist do?

- Be aware of signs and symptoms of iron overload
  - Often patients will self-treat and products that one may typically recommend are not ideal for patients with iron overload due to HHC.
- Is the person of Celtic or Northern European descent?
- Is there a history of severe liver disease, diabetes and/or arthritis in the family?
- Look to serum ferritin and transferrin saturation tests - not typically standard
What can the pharmacist do?

- Offer information & support:
  - for treatment of end organ disease,
  - management of medications pending which organs affected,
  - awareness of iron containing products
  - vaccinations
- Iron Tracker app - for phlebotomies
  
  http://www.irontracker.ca/
Mr. P. comes in to provide an update

- After 80 phlebotomies over 2.5 years, Mr. P. has successfully de-ironed and is on maintenance phlebotomies - every 56 days now as a blood donation
- He and his wife decided to get genetic counselling prior to starting a family.
- His 2 siblings have been tested and do not have HHC, some deceased relatives ?HHC
- He continues to have joint pain, which is a bit more involved - wrist
- His liver enzymes have normalized but his liver remains enlarged, he and his specialist have elected not to do a liver biopsy
- Still not taking regular prescriptions, you ensure that he is up to date on vaccinations,
The Canadian Hemochromatosis Society
https://www.toomuchiron.ca/

Classic Hereditary Hemochromatosis: NORD
https://rarediseases.org/rare-diseases/classic-hereditary-hemochromatosis/

National Institutes of Health: National Heart, Lung and Blood Institute
https://www.nhlbi.nih.gov/health-topics/hemochromatosis

Diagram for autosomal recessive disorders
https://en.wikipedia.org/wiki/Dominance_(genetics)


https://www.haemochromatosis.org.uk/Handlers/Download.aspx?idMF=0c5d81b6-146c-4885-9ec0-9f1ab59b3e2

Thanks to Mr. P. for permitting his story to be used as an illustration in this presentation