Provincial Blood Coordinating Program

Bloody Good News

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Newfoundland Labrador

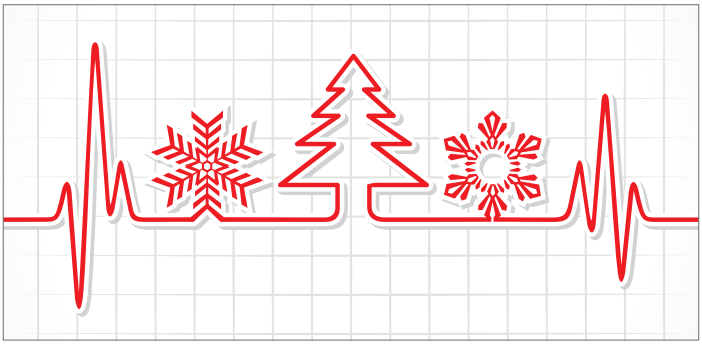
Christmas Disease

Christmas disease, also called Hemophilia B or factor IX (9) deficiency, was first reported in the medical literature in 1952 in a patient by the name of **Stephen Christmas**. This factor deficiency is a rare genetic disorder in which blood does not clot properly. Christmas disease causes the body to produce little or no factor IX which leads to prolonged or spontaneous bleeding. The lower the amount of factor IX produced, the worse the symptoms. If left untreated, Christmas disease can be fatal if an uncontrollable bleeding episode occurs.

The gene responsible for Christmas disease is carried on the X chromosome. Females have two X chromosomes and males have one X and one Y. If a male inherits the 'faulty gene' on his X chromosome, he will develop Christmas disease. If a female inherits the 'faulty gene' on one of her X chromosomes, she'll be a carrier for Christmas disease which means she may pass the 'faulty gene' on to her children. Females are usually only carriers because they have two X chromosomes. For a female to inherit Christmas disease, both of her parents would have to pass the 'faulty gene' on to her, which is very rare.

Female carriers may produce less factor IX than women who aren't carriers, which can result in mild abnormal bleeding after injuries or surgical procedures.

Severe cases of Christmas disease are usually diagnosed in babies during the first year of life. Testing may be precipitated by unexplained bleeding in the skull after childbirth and other spontaneous bleeding. Mild cases may not be diagnosed until a child reaches toddler years or sometimes even later. In all cases, diagnosis usually happens after abnormal bleeding from an injury or surgery. Other signs and symptoms may include unexplained, excessive bruising, prolonged



nosebleeds, unexplained blood in urine or feces caused by internal bleeding in the gastrointestinal or urinary tract, or by internal bleeding that pools in the joints, causing pain and swelling.

To diagnose a suspected case of Christmas disease a doctor will order a number of blood coagulation tests which may include:

- A factor IX test to determine how much of the specific clotting factor is present in the blood;
- An activated partial thromboplastin time (aPTT) test to measure how fast the blood clots;
- A prothrombin time (PT) test, which is another test to measure how quickly the blood clots; and
- A fibrinogen test to determine the body's ability to form a clot.

There is no cure for Christmas disease, but there are treatments available. Regular treatment is imperative for managing symptoms of a factor deficiency. One such treatment is factor IX injections or infusions to prevent or stop bleeding. Factor IX replacement is produced from donated human plasma or recombinant product made in a laboratory.

With treatment, most people with Christmas disease can live normal lives.

Merry Christmas and Happy New Year

from the Provincial Blood Coordinating Program!

Hereditary Angioedema

Hereditary angioedema (HAE) is a rare genetic disorder characterized by unpredictable and recurrent episodes of angioedema (swelling) in the gastrointestinal tract; peripheral, facial or genital cutaneous areas; or upper airway laryngeal area. HAE affects 1 in 50,000 people. The attacks occur due to a deficiency of C1 esterase inhibitor (C1-INH) either due to impaired production (Type I) or production of dysfunctional C1-INH (Type II). The deficiency of C1-esterase 'inhibitor' leads to overproduction of the vasoactive peptide bradykinin, causing vasodilation (dilatation of the blood vessels), increased vascular (blood vessel) permeability and angioedema.

There is also a Type III HAE characterized by normal C1-INH levels, however there is abnormal function of the gene which encodes coagulation factor XII thereby impacting normal bradykinin function. Type III mainly occurs in females.

Optimal management of HAE includes both prophylaxis and on-demand treatment of attacks. Depending on location, severity, and frequency of attacks, a prophylactic regimen may be implemented. Cutaneous HAE 'attacks' tend to be self-limiting. Abdominal attacks tend to be quite painful. Laryngeal attacks are potentially fatal due to the risk of intractable airway obstruction.

Short term treatment may be used prior to surgical, dental, or invasive procedures to prevent attacks.

Currently in Canada, two plasma derived C1-INH products are available for use; Berinert® approved for treatment of attacks and Cinryze® for prevention of attacks. Doses are administered intravenously at the onset of symptoms, requiring skill and expertise in reconstitution, preparation and administration. Icatibant or Firazyr® a selective and specific bradykinin B2 receptor is a drug approved by Health Canada for treatment of HAE attacks. Icatibant is self-administered subcutaneously in prefilled syringes. Time to onset of symptoms and treatment is much faster than with plasma-derived Berinert®.

Prognosis is variable. Prior to the availability of effective treatments, approximately one third of HAE patients died due to asphyxiation secondary to laryngeal edema. Attacks generally persist throughout the individual's life, however the frequency of attacks can be significantly reduced by therapy.

Case Study 26

A 64 year old female with past medical history of rheumatoid arthritis presents to ER with GI bleed. Patient reports several bouts of large amounts of hematemesis. Blood work reveals Hgb of 74. Patient is awaiting GI consult. Crossmatch is ordered for 4 units of red blood cells, with order to transfuse two units.

Vital signs pre first unit: Temp 36.5, Pulse 108, Respirations 18/minute, Blood pressure 96/72.

Patient receives first unit with no issues or significant change in vital signs noted. Upon receiving approximately 150 mLs of the second unit, the patient becomes increasingly short of breath, and respirations increase to 32/minute, Temp 36.8, Pulse 124, Blood pressure 120/84.

Transfusion was stopped; the prescriber and blood bank were notified. Adverse transfusion reaction workup was initiated and chest X-ray was completed as per prescriber order. Lasix 20 mg IV was given with good results noted (shortness of breath subsided, respiratory rate decreased 22/minute, increased urine output). Nothing notable from the workup and chest X-ray was normal.

What type of reaction has occurred? (Answer on last page.)

Hemochromatosis

A potential complication of chronic transfusion therapy

Iron storage in the body is a delicate balance. Hepcidin, a hormone secreted by the liver, normally controls iron absorption and usage in the body, as well as how any excess iron is stored in various organs. In hemochromatosis commonly referred to as 'iron overload,' chaos occurs when the normal role of hepcidin is disrupted, iron is increased, and the excess iron cannot be eliminated from the body. Hemochromatosis can be classified as primary or secondary.

Primary or hereditary hemochromatosis is caused by an inherited gene mutation which causes the body to absorb too much iron from food. The gene is a recessive gene so one must inherit the gene mutation from both parents for hemochromatosis to present; even then symptoms may or may not develop. Individuals who inherit only one mutated gene become a carrier of the disease. Many of those with primary hemochromatosis may not develop signs and symptoms until they reach their 50-60's. Women tend to show symptoms a little later (after menopause) as they lose some iron through menstruation and pregnancy.

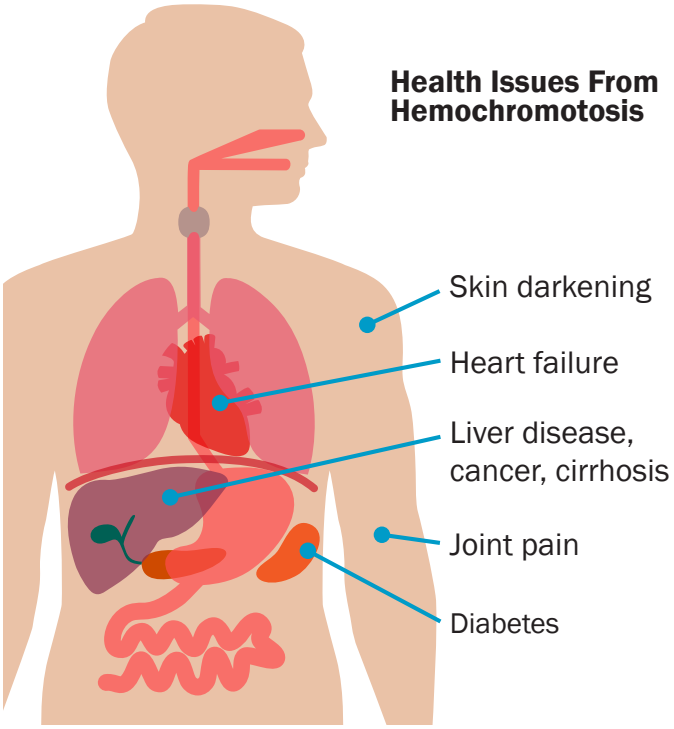
Secondary hemochromatosis refers to hemochromatosis resulting from a condition or treatment which causes an increase in the amount of iron in the body. The most common cause of secondary hemochromatosis is chronic transfusion therapy, secondary to a hematological condition. However, any patient who receives chronic transfusion therapy can potentially develop secondary hemochromatosis (burns, reoccurring GI bleed). Each unit of red blood cells contains about 200-250 mg of iron. Iron is normally lost daily in sweat and through the shedding of cutaneous and mucosal epithelial cells which equates to about 1 mg of iron a day. The body is not able to eliminate the excessive iron, so it accumulates. This explains how chronic transfusion therapy can lead to an iron imbalance.

Other factors which can lead to secondary hemochromatosis include chronic liver diseases (hepatitis C, alcoholic liver disease, and nonalcoholic steatohepatitis), long-term kidney dialysis, and iron supplements with or without vitamin C (which helps your body absorb iron) in individuals who do not require supplementation.

Signs and Symptoms

Signs and symptoms of hemochromatosis are the same regardless of etiology and include:

- Fatigue
- Hyperpigmentation
- General weakness
- Joint pain
- Weight loss
- Abdominal pain
- Hepatomegaly
- Frequent urination
- Hypogonadism and erectile dysfunction



Complications

Several significant complications may occur if hemochromatosis is not detected early and treatment initiated. These include permanent joint damage and pain; reproductive organ failure; underactive pituitary and thyroid glands; damage to the adrenal glands; glucose intolerance or diabetes mellitus especially in those with a family history; liver disease including cirrhosis, liver failure, and increased risk of hepatocellular carcinoma; and/or cardiomyopathy with heart failure.

Diagnosis
Laboratory testing and diagnostic imaging are used to confirm a diagnosis of hemochromatosis. Laboratory tests may include an iron series profile (which may include serum ferritin, iron, transferrin, and/or transferrin saturation), genetic testing (HFE gene for primary hemochromatosis), and liver function tests (to evaluate any potential liver injury).

Serum ferritin (SF) and transferrin saturation (TS) are of particular importance in the iron series profile. They reflect how much iron is in the body and how much is being transported and stored. Repeated elevations in both SF (greater than 200 ng/mL in women and 300 ng/mL in men) and TS (greater than 45%) are potential indicators of hemochromatosis and indicate a need for further investigation.

A diagnosis of hemochromatosis is often confirmed by imaging studies predominantly a MRI of the liver which will indicate the presence and amount of iron deposited in the liver.

Treatment
Treatment for both types of hemochromatosis is the same and includes therapeutic phlebotomy, iron chelation, and dietary changes. Therapeutic phlebotomy is very effective but may not be an option for everyone especially for those who are extremely fearful of needles and venipuncture or for those with secondary hemochromatosis which continue to have an anemia that requires transfusion therapy.

Iron chelators include deferoxamine, deferiprone, and deferasirox. These drugs must be given on a regular basis and are not effective when given intermittently. Deferoxamine involves a subcutaneous or intravenous infusion given over several hours several days a week. Due to the significant time commitment there is poor compliance with this regime. Deferiprone and deferasirox are both oral agents. Deferiprone has a short half-life and must be given three times daily to achieve an adequate dosing strategy whereas deferasirox is administered once daily. Both have different side effect profiles which may influence the prescriber's decision on which treatment to use.

Dietary changes may be beneficial in further reducing iron overload and minimizing signs and symptoms of hemochromatosis. Limiting vitamin C intake as this helps the body absorb iron from food. Avoid taking iron supplements or multivitamins containing iron (sometimes overlooked). Avoid uncooked fish and shellfish as it may contain bacteria which may cause infections in individuals with chronic health conditions, like hemochromatosis. Finally limiting alcohol intake as this can exacerbate any liver problems.

Prognosis
Prognosis is largely determined by how significant the disease is upon diagnosis and start of treatment. Poor prognostic factors include the development of cirrhosis, hepatocellular carcinoma, diabetes, and/or cardiomyopathy.

Conclusion
It is important to properly screen those who have received chronic transfusion therapy as it places them at higher risk of secondary hemochromatosis. This condition often goes undetected until permanent organ damage has resulted, so early detection and treatment is of paramount importance.

Case Study 26 Answer: Transfusion Associated Dyspnea (TAD). Signs, symptoms, and results of workup do not fit the diagnosis of Transfusion Associated Circulatory Overload (TACO) or Transfusion Related Acute Lung Injury (TRALI) and no preexisting medical condition present as possible explanation of symptoms.

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