ISSUE 10

The Bottom Line

Vaughan Endoscopy Clinic (VEC) is a **state of the art** out-of-hospital endoscopy clinic providing **Screening colonoscopy and endoscopy** for the work up of mild gastrointestinal disorders. It is staffed by gastroenterologists**.**

In addition to the endoscopic services, they will provide all the necessary **GI follow-up** and make all the appropriate referrals required due to findings at the endoscopy.

The Medical Director has been an active participant at the CPSO in the development of **standards for out-of-hospital clinics**, all of which VEC adheres to.

Gastroenterologists:
Dr. William Appell
Dr. David Ford
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Dr. Stephen Sinclair

In addition to high quality and convenient access to endoscopy, the doctors at VEC will provide you with supplemental practical GI advice through this periodic newsletter. This article is written by Dr. Eric Leong (a gastroenterologist from Humber River Regional).

Hereditary Hemochromatosis

Hereditary hemochromatosis is an inherited disorder of iron metabolism in which inappropriate intestinal absorption of iron occurs. Organ cells become progressively overloaded with iron and eventual multiorgan failure develops in untreated individuals. Major target organs include the liver, heart, pancreas, and pituitary gland. Untreated individuals are, therefore, at risk of developing cirrhosis, liver cancer, cardiomyopathy, cardiac arrhythmias, diabetes mellitus, and hypogonadotrophic hypogonadism. Individuals affected by hemochromatosis often feel fatigued and may experience symptoms of arthritis, as well as abnormal skin pigmentation.

Widely accepted criteria for the diagnosis of iron overload in the setting of hemochromatosis include being able to remove 4 g of iron by phlebotomy (16 units of blood) before the onset of iron-limited red blood cell production or at least one of the following liver biopsy results: grade 3 or 4 (out of four grades) stainable iron, liver iron concentration greater than 80 µmol per gram (dry weight) of liver tissue, and hepatic iron index (hepatic iron concentration divided by age) greater than 1.9. The identification of specific HFE gene mutations in individuals with hereditary hemochromatosis has allowed for genetic testing in clinical practice.

Hereditary hemochromatosis is inherited mostly in an autosomal recessive pattern. Approximately 85% of individuals with clinically expressed hemochromatosis have 2 copies of the C282Y mutation (C282Y homozygotes) and 3.3% have one copy of the C282Y mutation and one copy of the H63D mutation (C282Y/H63D compound heterozygotes). Individuals who have 2 copies of the C282Y mutation appear most likely to develop clinically significant iron overload, followed by C282Y/H63D compound heterozygotes. Iron overloading may be seen in individuals who have one copy of the C282Y mutation (C282Y heterozygotes), 2 copies of the H63D mutation (H63D homozygotes), and one copy of the H63D mutation (H63D heterozygotes), but the degree of iron overload is usually mild to moderate and substantially lower than in C282Y homozygotes.

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Genotypes and Expression of Hemochromatosis.

Genotype	Description	Iron-Overloaded Patients with Genotype	Degree of Phenotypic Expression
C282Y/C282Y	Homozygous for substitution of Tyr for Cys at position 282	85%	Severe iron-overload in up to 50%
C282Y/H63D	Compound heterozygote for substitution of Tyr for Cys at position 282 & Asp for His at position 63	3.3%	Severe iron-overload
C282Y/wt*	Simple heterozygote		Mild-to-moderate
H63D/wt*	Simple heterozygote		Mild-to-moderate
H63D/H63D	Homozygous for substitution of Asp for His at position 63		Mild-to-moderate

Asp = aspartic acid, Cys = cysteine, His = histidine, Tyr = tyrosine
*One Normal or "Wild Type" allele at this position to produce the heterozygote.
One in 300-400 Caucasians has clinically expressed hemochromatosis.

Many liver specialists recommend ordering serum transferrin saturation as part of the routine medical examination at about age 30. A value greater than 45% identifies 98% of affected individuals with hemochromatosis, with relatively few false-positive results. Serum ferritin should be checked in these individuals, recognizing that ferritin can be falsely elevated in the setting of infection, inflammation, or cancer. Serum ferritin provides a measure of the total iron burden.

Genotyping and measurement of liver enzymes should be performed in individuals in whom hemochromatosis is suspected on the basis of elevated iron indices. Non-HFE-associated causes of iron overload should be considered when the individual is not a C282Y homozygote or C282Y/H63D compound heterozygote. If the genotype, on the other hand, indicates predisposition to HFE-related hemochromatosis, serum ferritin and a liver enzyme profile should be followed with serial measurements.

Patients who have persistently elevated transferrin saturations with normal ferritin and normal serum AST and ALT levels have non-expressed hemochromatosis; clinical follow-up and repetition of the iron indices with serum AST and ALT levels in one to two years is reasonable in this setting. Phlebotomy should be performed in individuals whose ferritin is 300-1000 µg/L with normal liver enzymes.

Liver biopsy is necessary to confirm and identify the degree of iron overload when the patient has a serum ferritin greater than 1000 µg/L and/or elevated serum AST or ALT levels, as the risk of developing liver cancer and mortality rate increase substantially once the hepatic iron concentration is 400 µmol per gram or more. However, young patients under 40 years of age who are genetically at risk for expressing hemochromatosis are unlikely to have significant scar tissue formation in the liver and liver biopsy may be unnecessary in this group.

The bottom line is:

Hereditary hemochromatosis is a relatively common inherited disorder of iron metabolism and should be considered in any individual presenting with elevated liver enzymes, transferrin saturation greater than 45%, or any of the symptoms or clinical conditions listed above.

Our newsletters are posted on our website (www.vaughanendoscopy.com) thus your patients are able to download a copy for reference. Other GI topics of interest are published periodically.