HAMILTON REGIONAL LABORATORY MEDICINE PROGRAM

LAB CONNECTIONS

January 2011 / Issue #111

IN THIS ISSUE:

Andrew McFarlane and Karen Moffat describe hereditary hemochromatosis and the situations when genetic testing may be needed.
Efforts to reduce errors in specimen labeling are ongoing. Follow the link in the *"Quality Snapshot"* to learn how to avoid errors.
New in this issue is the rounds schedule for Anatomical Pathology. These are CME accredited.

WHAT'S NEW?

- When is DIC screen or D-dimer testing required? D-Dimer memo
- Is ESR the best test to assess severity of inflammatory responses? ESR CRP memo
- Molecular testing for RSV is now available. Multiplex Resp PCR

Laboratory Diagnosis of Hereditary Hemochromatosis: The role of genetic testing.

Iron is essential for erythropoiesis, oxygen transportation and cellular immune responses. Iron homeostasis is maintained through strict regulatory systems that conserve and recycle existing stores as well as control the absorption of dietary iron for replacement of daily losses. Normally, iron is bound to transferrin and ferritin in a nonreactive state. However, in its unbound form, free iron radicals are toxic agents for tissues and organs. Excessive plasma iron levels and iron overload can result from a number of acquired or genetic factors resulting in the eventual deposition in tissues and organs. Much research has led to a good understanding of iron homeostasis, especially with the discovery of the HFE gene mutations associated with hereditary hemochromatosis where dysregulation of iron absorption and cellular iron release leads to iron overload (1).

Genetics of Hereditary Hemochromatosis

Several gene mutations have been well defined in the HFE gene since it was first identified in 1996 on chromosome 6. These HFE mutations are classified as hereditary hemochromatosis type 1. The two most common mutations identified are C282Y and H63D (Cys282Tyr and His63Gly). Individuals who inherit two C282Y mutations (one from each parent) are called C282Y homozygotes (C282Y/C282Y). Ten to thirty percent of homozygotes may eventually develop hemochromatosis-associated morbidity with men having a higher risk than women. This genotype may also be associated with iron overload. Due to this low prevalence, a diagnosis of hemochromatosis does not rely on identification of C282Y homozygosity.

/cont'd

YOUR FEEDBACK IS VALUED!

Your feedback, suggestions and new ideas are most welcome!

Approximately eighty percent of all hereditary hemochromatosis cases are C282Y homozygotes. Patients who inherit a C282Y mutation from one parent and a H63D mutation from the other parent are called compound heterozygotes (C282Y/H63D) and account for approximately five percent of all hereditary hemochromatosis cases. The majority of compound heterozygotes will never develop clinical iron overload nor will a heterozygous patient who has only the one gene C282Y mutation. Other rarer HFE mutations have also been described including the S65C mutation, but the majority of these mutations are not associated with a clinically severe hemochromatosis phenotypes (2).

Hereditary hemochromatosis rarely results from gene mutations in other proteins that are involved in iron absorption, transport and/or storage.

Other genes known to carry mutations associated with hereditary hemochromatosis include:

- Heomojuvelin (HJV) -Juvenile hemochromatosis type 2a
- Hepcidin (HAMP) - Juvenile hemochromatosis type 2b
- Transferrin Receptor 2(TfR2) - type 3
- Ferroportin – type 4 (ferroportin resistant to the effect of hepcidin)
- Hereditary aceruloplasminemia
- Dimetal transporter mutations (DMT1)

Diagnosis of hereditary hemochromatosis:

The correct diagnosis of iron overload involves a sequential approach. Clinical evaluations where hemochromatosis is suspected should have biochemical screening tests to confirm increased total body iron. The most useful tests include: serum iron studies, TIBC, transferrin saturation and ferritin. In most cases, a normal transferrin saturation will exclude iron overload. Experts agree that further genetic tests to identify the HFE mutations confirming type 1 hemochromatosis is warranted only when patients have elevated levels of transferrin saturation (>45%) and ferritin (>200 ng/ml in women, >300 ng/mL in men) (1,2). Recent studies demonstrated that up to 90% of men and 75% of women who had persistently elevated transferrin saturation and hyperferritinemia were homozygous for the C282Y mutation (2). The most current practice guidelines do not recommend genetic testing in asymptomatic individuals (2,3).

A retrospective review of HFE genotyping requests received in the last 5 years by the HRLMP Molecular Hematology laboratory was done to assess whether the test requests met with current published clinical practice guidelines. The results suggest that ordering practices are not following the current recommendations for the diagnosis of HFE-associated hereditary hemochromatosis. Over the next few months, changes will be implemented to assure current recommended practice guidelines are followed and to improve test utilization for the diagnosis of hereditary hemochromatosis.

Testing for genetic mutations for other non-HFE types of hemochromatosis are currently not available in the HRLMP. Therefore, the diagnosis of non-HFE hemochromatosis relies on clinical correlation and laboratory evidence along with elevated liver iron concentrations in the absence of acquired causes (1).

References:

1) Manuel Muñoz, José Antonio García-Erce and Ángel Francisco Remacha (2010) Disorders of iron metabolism. Part II: iron deficiency and iron overload *J Clin Pathol* published online December 20, 2010 (Available from: http://jcp.bmj.com/content/early/2010/12/20/jcp.2010.086991.full.html)
2) European Association for the Study of Liver (2010) "EASL clinical practice guidelines for HFE hemochromatosis" Journal of Hepatology 2010 vol. 53 j 3–22.
3) Qaseem A et al. Screening for hereditary hemochromatosis: A clinical practice guideline from the American College of Physicians. Ann Intern Med 2005 Oct 4; 143:517-21.

Mr. Andrew McFarlane, FCSMLS(D),Technical Specialist Molecular Hematology and Genetics, and Ms. Karen Moffat, FCSMLS(D), Technical Specialist Coagulation, Hamilton Regional Laboratory Medicine Program.

QUALITY SNAPSHOT:

Document and Record Control and Equipment Management

"If the process is right, the results will take care of themselves"
– Takashi Osada

How many times have you started to read a newspaper or magazine in a waiting room only to realize it is out of date?

With over 8300 approved documents in use across HRLMP, document control and managing change are essential, particularly as the rate of change continues to increase. These documents provide a wide range of content from individual test methods, quality assurance procedures and equipment or instrument operation used by our staff, to specimen handling and collection instructions used by our clinical partners. The goal of document and record control within a Quality Management System is to provide the most current information for use to those working within the system as they are a tool used to communicate what we do and how we do it. Ensuring that the process or procedure is "right" is critical to the maintenance and improvement of our standards of practice.

Equipment management is another essential component of our Quality Management System. The HRLMP has approximately 2400 pieces of equipment in use ranging from complex multi-analyte instruments to the most basic of instruments such as a pH meter. All of our instruments have been standardized where possible to reduce variability of our test results and minimize training requirements. In order to produce over 10 million quality test results each year, our instruments must be continually maintained and quality controlled for optimal performance.

Prior to use, all equipment enters a qualification process that ensures the equipment:

- Meets manufacturers' performance claims
- Is suitable for its intended use
- Operation is understood by all users
- Meets safety and quality standards and requirements
- Is stored and operated in appropriate and controlled conditions
- Is cost effective to satisfy all of the above points

Taking the time to properly develop, validate and implement documents and equipment prior to use ensures that the "process is right" and the HRLMP is able to produce *accurate, reproducible and clinically relevant test results*.

References:

1. CLSI [Formerly NCCLS]. CLSI document HS1-A2 – A Quality Management System Model for Health Care; Approved Guideline – Second Edition. Wayne (PA); Clinical and Laboratory Standards Institute; 2001

Cathie McCallum, Quality Manager, HRLMP, and
Tom Dorland, Quality Specialist, HRLMP

HRLMP Lab Patient Quality and Safety Update –

The Usual Suspects – Specimen Labelling Guide

EDUCATION:

Training Programs:

For information and the latest news on our residency training programs please follow the link: http://www.fhs.mcmaster.ca/pathres/news/index.html
Information on the postdoctoral fellowship training program can be obtained by following the link:
http://fhs.mcmaster.ca/pathology/education/postdoctoralfellowshiptraining.htm/

Anatomical Pathology Lectures:

Rounds Schedule for remainder of the year:

TIME: 12:30 – 1:30 P.M.

DATE: 2011	SPEAKER:	TOPIC:
February 17th MDCL - 3023	Dr. M. Tarnopolsky, McMaster University	Clinico – Pathological correlates of mitochondrial disease.
April 7th MDCL – 3024	Dr. S. Nofech-Mozes, University of Toronto	Cancer stem cells in different molecular subtypes of breast cancer
June 16th MDCL - 3023	Dr. M. Sur, HRLMP – McMaster University	Hematopathology - TBA

ANATOMICAL PATHOLOGY GRAND ROUNDS ARE SPONSORED BY THE DEPARTMENT OF PATHOLOGY AND MOLECULAR MEDICINE ROYAL COLLEGE ACCREDITATION

Contact person re: Pathology Rounds Schedule:

Cindy Campbell
Electron Microscopy
Administrative Assistant
MUMC - 2V17
Phone: 905-525-9140 / Ext. 22496
Fax: 905-577-0198
campbelc@hhsc.ca