MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
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Clinical Research Centre

NETWORK

Familial Gastrointestinal Cancer Registry

Winter 2009

CLINICAL FOCUS

Juvenile Polyposis

Carol Durno, MD, MSc
Registry Pediatric Gastroenterologist

People can have many polyps in the gastrointestinal tract. The type and number of polyps found help determine what polyp condition the person has. People with at least five "juvenile" polyps may have Juvenile Polyposis (JP). "Juvenile" refers to the **histology** (microscopic study of tissue) of the polyp and not the age of the person. Adults also have juvenile polyps.

Patients with JP may experience painless rectal bleeding. The bleeding can occur during childhood, adolescence, or adulthood. Some patients have **anemia** (low red blood cell count). A patient with JP may have no symptoms. It is important to find out if a person has JP because the risk of developing colon cancer is greatly increased. Recent studies show a 40% risk of developing colon cancer. Some patients with JP can have associated conditions such as heart abnormalities or bleeding tendencies which indicate Hereditary Hemorrhagic Telangiectasia or HHT. Patients may have been born with heart defects which require surgery. The Registry is evaluating patients with JP who have HHT. The syndrome is referred to as JP-HHT. We are working with registries around the world to study this population, research which will help in our understanding. If you or your family members have JP and you think you may have family members who show characteristics found in HHT, it is important to let your doctor know or contact the Registry, 416-586-4800 ext. 8334.

JP is a genetic condition. Research has shown that a gene **mutation** (change in a gene capable of being transmitted from parent to child) can be found in about 40% of patients with JP. Examples of gene mutations found in JP are named *BMPR1A* (located on chromosome 10) and *SMAD4* (located on chromosome 18). Ongoing research is looking for more genes that can cause JP. If a family member has JP, each child will have a 50% chance of developing JP. The genetic testing which is a blood test is completed in specialized laboratories. Part of the work of the Registry is to organize genetic counselling and testing for people with JP. If a specific mutation is identified, other family members at risk of developing JP can be screened for the same mutation with a blood test. Only a blood test can determine if a person carries the mutation.

Some families may not know they have JP. JP families may have a history of many members with colon cancer. Families with colon cancer occurring in young individuals (less than 50 years) need to have careful evaluation to determine if there is a genetic reason behind the colon cancer. The Registry evaluates families to determine the cause of the cancer. Evaluation of other polyps in patients with colon cancer may raise the possibility of JP as the underlying cause. Depending on the results, genetic testing for JP may be suggested. Sometimes a child may be the first person in a family to be diagnosed with JP. When a child is diagnosed with JP, the parents should also be evaluated for JP because they have a 50% risk of carrying the mutation and may have no symptoms. Even if only one person in a family is found to have JP, that individual still has a 40% risk of developing colon cancer.

Screening for JP by **colonoscopy** (examination of the large bowel) and **gastroscopy** (examination of the stomach and first part of the small intestine) is recommended starting in the mid-teens or when symptoms develop. The frequency is determined by the number of polyps and particulars of the **histology** (microscopic examination of the tissue) in a given person. Some patients with JP have polyps removed through the colonoscope. In certain cases, surgery to remove a section of bowel is recommended. Patients with a *SMAD4* mutation are more likely to develop polyps in the stomach which require treatment. Medication trials are being designed to evaluate medications which may prevent polyp formation.

Patients with JP require long-term follow-up by a gastroenterologist or a surgeon due to the increased risk of cancer.

HHT and Juvenile Polyposis

Marie E. Faughnan MD
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What Is HHT?
Hereditary Hemorrhagic Telangiectasia (HHT) is a hereditary disorder which affects the development of blood vessels. It affects both males and females from all racial and ethnic groups and occurs in approximately one in 5,000 individuals. A link has recently been discovered between HHT and Juvenile Polyposis. A small number of families have both of these disorders, inherited together, with a mutation in the *SMAD4* gene. The *SMAD4* gene is a typical JP gene. Though we don't know the exact numbers yet, it seems that a small percentage of the JP families with *SMAD4* mutation also have HHT. So far, it seems that approximately 3% of the HHT families have JP.

HHT is characterized by the presence of abnormal blood vessels. The small abnormal blood vessels are called telangiectases (Figure. 1). These vessels lack a capillary bed, and therefore each telangiectasia is a direct connection between an artery and a vein. They appear as small red spots on the skin or the lining of the mouth (Figure 2) and nose that may be as small as a pinpoint or as large as a pea in size.

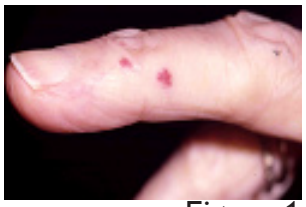


Figure 1

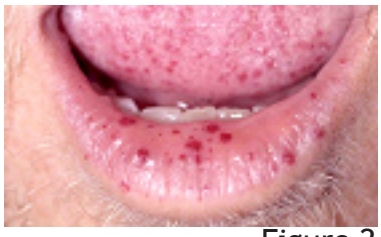


Figure 2

When the abnormal blood vessels are larger, they are called **arteriovenous malformations** (AVMs). AVMs can develop in the body organs, especially the lungs and brain.

Telangiectasia and AVMs are fragile and so have a tendency to bleed. They can also cause other serious complications, such as stroke and heart failure. The good news is that most of these complications can be prevented with screening and treatment of AVMs in patients with HHT.

How Does HHT Affect A Person?
The location of telangiectasia or AVMs will determine how HHT will affect an individual. Approximately 90% of adults with HHT will have recurrent nosebleeds and have telangiectases on the skin of the hands, face, or in the mouth. Many patients with HHT will have iron-deficiency anemia due to chronic blood loss from the nose. Approximately 20% of adults with HHT will also have some chronic bleeding from telangiectases in the stomach and small bowel. Approximately 30% of people with HHT will have AVMs in the lungs and 10% will have AVMs in the brain. The lung and brain AVMs put patients at risk of stroke as well as bleeding. Most HHT patients will have telangiectases in the liver but only rarely do these cause symptoms. Children can have HHT too, as it is an inherited disorder, but the symptoms and complications are less frequent in children.

Can HHT Be Treated?
Yes. Although there is not yet a way to prevent telangiectases or AVMs from developing, most can be treated to prevent complications. Most organ AVMs are treated with high-tech minimally invasive treatment through the blood vessels. The exact type of treatment depends on the size and location of the AVMs.

When To Consider HHT?
It is important to consider HHT if someone has recurrent nosebleeds, as well as a family history of nosebleeds, especially if they have telangiectasias. A history of organ AVMs in several family members is also very suggestive.

Is Genetic Testing Available For HHT?
Genetic testing for HHT is available. It is primarily used for the relatives of an HHT patient, to determine who has inherited HHT. Currently two genes have been identified as causing HHT, Endoglin and ALK-1. These genes do not appear to be associated with JP. SMAD4 testing is also available for HHT families, as well as JP patients and families with the suspected combined syndrome.

Resources
Detailed information about HHT can be found at the HHT Foundation International Web site www.hht.org.

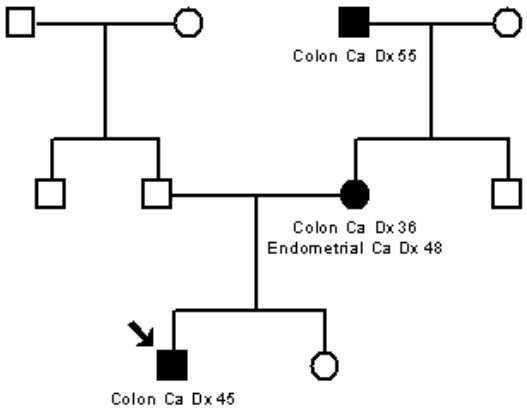
There are four Canadian Specialized HHT Centres, in Toronto (www.hhttoronto.com), Montreal, Edmonton and Vancouver.

RESEARCH CORNER

New Gene in Lynch Syndrome

Dr. Bharati Bapat, PhD
Department of Pathology and Lab Medicine

Lynch Syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is a form of genetic susceptibility to early-onset colorectal cancer. Patients with LS carry an increased risk of developing cancer of the **endometrium** as well as other gastrointestinal and gynecologic cancers such as small bowel, kidney, stomach, pancreas and ovarian. LS is caused by **mutations** in a group of genes: *MSH2*, *MLH1*, *MSH6*, and *PMS2*.



Studies are ongoing to identify other genes responsible for LS. New research published in 2009 by Dutch and Chinese scientists found that some people with LS have large deletions within the *EpCAM* or *TACSTD1* gene. *EpCAM* resides beside the *MSH2* gene, which has already been established to be involved with LS. These large deletions in the *EpCAM* gene prevent the *MSH2* gene from carrying out its normal function, and in turn cause LS. In essence, these *EpCAM* mutations "silence" the *MSH2* gene and lead to the appearance that *MSH2* is the problem. Since research revealed this phenomenon, clinical genetic testing is now available to look for *EpCAM* deletions.

International Research Opportunity for Registry Families

Spring Holter, MSC
Genetic Counsellor

Families who have previously participated in the Registry may now be eligible to take part in an international collaborative colorectal cancer research study. The Ontario Familial Colorectal Cancer Registry (OFCCR) is part of the Colon Cancer Family Registries which has four sites in the United States and one site in Australia. The OFCCR has been recruiting individuals with colorectal cancer and their family members since 1997. The OFCCR provides a resource for researchers around the world to look at the genetics and other causes of colorectal cancer.

Phase III of the OFCCR will be recruiting families who were first involved in our Registry and other cancer genetics clinics around Canada (British Columbia, Alberta and Newfoundland). If you or your family members are already Registry participants, we are asking that you allow us to add your family's information to the OFCCR. Most of the information and blood and/or tumour samples that you may have already provided can be used by the OFCCR, so you may not be asked to repeat these steps.

Who do we want to recruit?

- Families with a mutation in a Lynch syndrome gene: *MLH1, MSH2, MSH6* or *PMS2*
- Families with MYH-Associated Polyposis (MAP)
- Families with 3 or more first-degree relatives (parents, siblings or children) with colorectal cancer who do not have a known hereditary condition, at least two successive generations affected and at least one cancer diagnosis must be under 50 years of age

What does participation involve?

- The staff at the OFCCR will contact you to review your family history and give you more information about the OFCCR
- You will be asked to sign consent forms agreeing to participate in the OFCCR. This study has been approved by the Mount Sinai Hospital Research Ethics Board
- If you have had cancer, the OFCCR would request medical records to confirm this diagnosis. These records may already be in the Registry and we could transfer a copy of them to the OFCCR with your permission
- You will be asked to complete a questionnaire about possible risk factors for colorectal cancer
- You will be asked if other family members may be interested in participating. If so, we ask for your permission to contact them
- If you have already given a research blood sample to the Registry, this can also be used for the OFCCR. Most individuals will not have to have a new blood sample drawn, although some participants may need a new blood sample

What are the risks and benefits of participating in the OFCCR?

- You will have the opportunity to contribute to our understanding of cancer and its causes
- You or your family members might choose to participate in future studies of cancer prevention or early detection
- You and your family may find it emotionally distressing to recall and discuss past illnesses and deaths in the family
- Your and other family members may disagree about whether to be part of this research

While we would be most grateful for your help in this research, your participation is completely voluntary. Non-participation will not affect any current or future medical care and you will continue to receive best available monitoring and care. If you are interested in learning more about the OFCCR, please feel free to contact Spring Holter, genetic counsellor, at 416-586-4800 ext. 2088 or sholter@mtsinai.on.ca.

Calling All Teens with FAP

In the Summer 2007 issue, we told you about a new study for teens with FAP to learn more about their experiences after their diagnosis with follow-up and daily life. We are interested in better understanding what teens feel is important to newly diagnosed patients. Volunteers will be asked to complete a questionnaire and can contact Terri Berk at 416-586-4800 ext. 8334 or tberk@mtsinai.on.ca.

NEWSFLASH

Melyssa Aronson, MSc, CGC
Genetic Counsellor

ABC's Primetime news did a story on 11 cousins who had surgery to remove their stomachs in an effort to prevent stomach cancer. What would put these cousins at such high risk for developing stomach cancer?
http://abcnews.go.com/GMA/OnCall/story?id=2096737

The answer was a hereditary disease running through the family that increased the risk to develop stomach cancer, also known as **gastric cancer**. The name of this syndrome is Hereditary Diffuse Gastric Cancer Syndrome or HDGC.

Overall, gastric cancer is a fairly common cancer worldwide, seen more commonly in Latin and Asian countries such as Japan, and more rarely in North America, with Ontario having one of the lowest rates in the world.

It occurs more commonly in men than women, and has been associated with various risk factors including diets high in pickled, cured, salted, smoked food and lower in fruits and vegetables; smoking; alcohol consumption; a blood condition known as pernicious anemia; and other environmental factors (e.g. asbestos). It has also been strongly associated with infections caused by a bacteria found in the stomach and intestinal tract known as Helicobacter pylori (**H. pylori)** bacteria.

Most cases of gastric cancer are **sporadic** (not inherited from parents). It is thought that less than 5% of patients with gastric cancer have an inherited form of the cancer. HDGC is caused by a mutation in a gene known as *CDH1*. We each have two copies of the *CDH1* gene, one we inherit from our mother and the other we inherit from our father. If a person is born with a mutation in this gene (from either mother or father), he/she will have HDGC and be at a much higher risk to develop a specific kind of stomach cancer known as diffuse-type gastric cancer. It has been estimated that the lifetime risk to develop gastric cancer in patients with HDGC is around 8,0%. The average age of onset in both men and women is 38 years old, although it has been seen at younger ages in some individuals with HDGC. Patients with HDGC are also at a higher risk to develop a specific kind of breast cancer which forms in the lobules of the breast, called **lobular breast cancer.** Researchers are still investigating whether any other types of cancers are increased in these families.

Unfortunately, HDGC cannot be cured and due to the aggressive nature of gastric cancer, there are no effective screening tools to detect it at an early stage. For patients with confirmed *CDH1* gene mutations, surgery to remove the stomach is recommended. Breast cancer screening would also be recommended.

There are about 100 families with HDGC, just like the one described on ABC's Primetime. Our Registry currently follows a number of these families and provides genetic testing, counselling, support, and referrals for screening and surgery. Our genetic counsellor, Melyssa Aronson, specializes in families with gastric cancer. "One issue that I discuss with families is that genetic testing has to be done using a blood sample from a relative who has gastric cancer. Often, a family will ask us to urgently obtain a sample from a relative, even though the family is not ready to pursue genetic testing. We are able to bank samples for the family and we remain available to those families for support and when they are ready, we can provide information on screening and genetic testing."

If a family has numerous relatives with gastric cancer, or a relative diagnosed at a young age with gastric cancer (under 40), or a history of lobular breast and gastric cancer, please contact us at 416-586-4800 ext. 3154 so we can better assess the family.

If you want to learn more about HDGC, please go to our Web site at: http://www.mountsinai.on.ca/care/fgicr/diseases/

REGISTRY UPDATE

1. From June 23-27th, 2009, the International Society for Gastrointestinal Hereditary Tumours met in Dusseldorf, Germany. This organization includes Registry members from different disciplines around the world who come together every two years to share new research for inherited gastrointestinal cancer. For example, a project is underway to classify over 10,000 genetic variants in mismatch repair genes which have been identified in 2009 in research and clinical laboratories. One of the goals is to separate mutations which are not disease-causing. This information, along with medical and family history, will be a comprehensive and invaluable resource. For rare genetic disorders, collaborative studies will help identify the risk to affected families.

2. From October 17-18th, 2009, the Collaborative Group of the Americas on Inherited Colorectal Cancer held its annual meeting in Honolulu, Hawaii. This meeting presents clinical updates and new research findings in hereditary colorectal cancer.

CAPP2 Findings and Plans for CAPP3

The second phase of the Colorectal Adenoma/Carcinoma Prevention Programme (CAPP2) evaluated the effects of aspirin and/or resistant starch in preventing colorectal adenomas and cancer in individuals with Lynch syndrome/HNPCC. Previous reports in December 2008 showed that there was no difference in polyp/cancer development between the treatment and placebo groups. Longterm follow-up (mean: 51 months) data is now available for 667 participants. Analysis shows that there is a significant reduction in the cancer incidence in the group receiving aspirin. This effect has been shown to be most significant in individuals who were treated with aspirin for 24 months or longer. This data shows that aspirin may be a viable drug for individuals with Lynch syndrome.

A new study, CAPP3, is currently in development. This study hopes to look at different doses of aspirin in Lynch syndrome patients to determine the most effective dose. Lynch syndrome carriers from the Registry participated in CAPP2 and most likely will be offered participation in CAPP3 once it begins.

New Regions for Colorectal Polyps and Cancer Found

Research groups at the Huntsman Cancer Institute in Utah and the Queensland Institute of Medical Research in Australia have identified two different areas in our genome that may lead to the discovery of new colorectal cancer genes. The Huntsman group identified a new region on chromosome 13 that is linked to individuals with colorectal cancer and precancerous polyps called **adenomas**. The Queensland group has identified an area on chromosome 2 in families with polyps and colorectal cancer. These are preliminary results and the groups are currently looking for the specific gene(s) in this area which may explain the colorectal cancer and polyps found in these families.

UPCOMING EVENTS

Education Night for Lynch Syndrome Families

Lynch syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer or HNPCC) is a rare genetic condition that greatly increases the risk to develop cancer, primarily colorectal and endometrial cancer. At one time, it was thought that all colorectal cancer followed a similar pathway to becoming cancerous, but we now know that this is not the case. While most lectures on colorectal cancer refer to the general population, talks for families with Lynch syndrome should be tailored to the research on risk, screening, and treatment of cancers in these families.

It was for that reason that the biennial education night for patients with Lynch syndrome was created. We began hosting this night in 2003 and have invited surgeons, a gastroenterologist, gynecologist, pathologist, family physician, dermatologist, and psychotherapist to update our families on the latest research and understanding of this syndrome. We also invited patients with Lynch syndrome to share their stories, which were always greatly appreciated by the audience.

Once again, we plan to host the 4th biennial education night in the spring. More details on the speakers for this night, along with the date and time will follow. If you have not received a mailing about this Education Night in the past, and are interested in attending, please feel free to contact us at 416-586-4800 ext. 5112, and we can add you to the mailing list designed for this evening.

Left to Right: Salah Metwaly, Dr. Zane Cohen, Kara Semotiuk, Spring Holter, and Melyssa Aronson, Harden Huang

GLOSSARY

Adenoma – precancerous polyp.

Anemia – low red blood cell count.

Arteriovenous malformation – larger abnormal blood vessels which may develop in the lungs or brain.

Colon – large bowel, about 1.5 meters or 5 feet long.

Colonoscopy – flexible tube and optical system as well as a snare to remove tissue from the large bowel for examination under the microscope.

DNA - complext protein which is arranged as two long chains twisted around each other; the chemical basis of heredity and the carrier of genetic information.

Endometrium – lining of the uterus.

Familial adenomatous polyposis – genetic disorder of the gastrointestinal tract characterized by up to 100 or more precancerous polyps in the colon.

Gastroscopy – flexible tube with an optical system to examine the stomach and first part of the small intestine and a snare to remove tissue.

Gene – a specific unit of DNA which contains instructions for the body to grow, develop, and function.

Germline – blood DNA.

Helicobacter pylori – bacteria found in the stomach and intestinal tract.

Hereditary Diffuse Gastric Cancer Syndrome – genetic form of stomach cancer.

Hereditary Hemorrhagic Telangiectasia – genetic disorder which affects the development of blood vessels.

Hereditary Non-Polyposis Colorectal Cancer – see Lynch Syndrome.

Histology - microscopic study of tissue.

Juvenile polyposis – genetic disorder of the gastrointestinal tract characterized by 5 or more polyps which are generally an overgrowth of normal tissue but may be precancerous. There is an increased risk of birth defects involving the bowel, heart, or central nervous system.

Lobular breast cancer - specific kind of cancer which forms in the lobules of the breast.

Lynch syndrome – genetic disorder in which people are at increased risk of cancer of the large bowel, endometrium, and other associated cancers.

MYH-Associated Polyposis – genetic disorder of the gastrointestinal tract characterized by 10 or more precancerous polyps in the colon.

Mismatch repair genes – genes that detect and repair “spelling” mistakes that occur during DNA replication.

Mutation – change in a gene capable of being transmitted from parent to child.

Sporadic – not inherited from parents.

Telangiectasia – abnormal blood vessels.

NETWORK

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