MEDIBEATS
The Medical Bulletin

Syndrome

Lynch Syndrome Definition:

- Lynch syndrome also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common cause of hereditary colorectal (colon) cancer.
- There is also an increased risk of developing other types of cancers, such as endometrial (uterine), gastric (stomach), ovarian, small bowel (small intestines), pancreatic, prostate, urinary tract, kidney, bile duct and brain cancers.

History :

- Lynch Syndrome was initially recognized by the University of Michigan pathologist A.S. Warthin in 1913.

Etiology :

- Lynch syndrome is due to inherited changes (mutations) in genes that affect DNA mismatch repair, a process that fixes mistakes made when DNA is copied.
- These genes (MLHL, MSH2, MSH6, PMS2, and EPCAM) normally protect you from getting certain cancers, but some mutations in these genes prevent them from working properly.
- Everyone has two copies of each of the genes involved in Lynch Syndrome, one from their mother and one from their father. Even if a person inherits a mutation in a Lynch syndrome gene, they still have the normal copy of the gene from the other parent.
- Cancer occurs when a second mutation affects the normal working copy of the gene, so that the person no longer has a copy of the gene that works properly.
- Unlike the inherited Lynch syndrome mutation, the second mutation would not be present throughout the person's body, but would only be present in the cancer tissue.
- However, not everyone with Lynch syndrome will get cancer.
- Colorectal cancer also can be caused by mutations in genes other than those related to Lynch syndrome.

Epidemiology :

- Lynch syndrome accounts for 2% to 4% of all colorectal cancer cases and approximately 2.5% of endometrial cancer cases. Signs : A set of criteria called the Amsterdam II Criteria & revised Bethesda guidelines are used to decide who should be tested for Lynch syndrome: A. Amsterdam II Criteria More than three relatives with a Lynch syndrome-related cancer

(colorectal, endometrial, small bowel, ureter or renal pelvis), with one being a first that meet the following criteria:

- More than two successive generations affected
- One is a first-degree relative of the other two
- More than one relative is diagnosed younger than age 50
- No evidence of Familial Adenomatous Polyposis (FAP) B. Revised Bethesda Guidelines
- Colorectal cancer diagnosed in a patient younger than age 50
- Presence of synchronous or metachronous, colorectal, or other Lynch syndrome-related tumors*, regardless of age
- Colorectal cancer with microsatellite instability-high histology (tumor infiltrating lymphocytes, Crohn like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern)
- Colorectal cancer diagnosed in a patient with one or more first-degree relatives with a Lynch syndrome-related cancer*, with one of the cancers diagnosed before age 50
- Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with Lynch syndrome-related cancers* regardless of age.

Diagnosis :

- The two methods used to screen for Lynch syndrome are immunohistochemical staining and/or microsatellite instability testing.
- Clinical Testing Criteria (based on personal and family history) - Assessment for Lynch syndrome begins with taking a thorough family cancer history, which includes both maternal and paternal relatives and at least three generations made up of first, second, and third-degree relatives.
- Genetic testing for Lynch syndrome should be considered for patients who meet:
  - Amsterdan II criteria
  - Revised Bethesda guidelines
  - Endometrial cancer diagnosed before age 50
  - Known Lynch syndrome in the family
- Testing should also be considered in patients with at least 5% risk of Lynch syndrome on MMRpro, PREMM, or MMRpredict prediction models

Screening :

Recommended surveillance for Lynch syndrome carriers is outlined as follows:

- Colonoscopy beginning at age 20 to 25 repeating every one to two years; or two to five years before the earliest colorectal cancer if diagnosed before age 25 years.
- Colectomy can be performed if colon cancer is diagnosed or if an advanced adenoma is found that cannot be otherwise removed.
- Follow-up surveillance with lower endoscopic examination is suggested every one to two years postoperatively.
- Endometrium (Uterus) and Ovaries in females.
- Pelvic exam, transvaginal ultrasound, endometrial aspiration and/or CA-125 can be considered on an individual basis. The efficacy of this regimen remains uncertain.
- Any abnormal uterine/vaginal bleeding warrants immediate evaluation.
- Hysterectomy with Salpingo-Oophorectomy (Females) recommended when childbearing is complete
- Other Extracolonic Cancers (**MLH1, MSH2 and EPCAM mutation carriers only)
- Upper endoscopy (esophagogastroduodenoscopy) with extended duodenoscopy every three to five years beginning at age 30 to 35 years can be considered in select individuals or families or those of Asian descent. Consider testing and treating for H. Pylori.
- Urinalysis, consider beginning annually between age 30 to 35. (The optimal age to begin screening for urinary tract cancers has not been determined, but the risk for developing such types of cancer before age 30 years is low).
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- The efficacy of non-steroidal anti-inflammatory drugs in individuals with Lynch syndrome is under investigation. There is data suggesting aspirin use may decrease the risk of colon cancer in Lynch syndrome, but the optimal dose and duration remains uncertain.

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