Ref: Ro Med J. 2022;69(Suppl3)
DOI: 10.37897/RMJ.2022.S3.16

Lynch syndrome in endometrial cancer

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ABSTRACT

In this article, we will present Lynch syndrome type I/HNPCC (hereditary non-polyposis colorectal cancer, the subtypes and generalities about Lynch syndrome type II, and the rarer variant, Muir-Torre Syndrome (MTS). In addition, we discuss the importance of suspecting this syndrome in endometrial cancer and the genetic testing needed to confirm this diagnosis.

Keywords: Lynch syndrome, endometrial cancer, screening, MSH

INTRODUCTION

Lynch syndrome also known as HNPCC (hereditary non-polyposis colorectal cancer) is an autosomal dominant disorder characterized by germline pathogenic variants in mismatch repair genes such as MLH1, MSH2, MSH6, PMS2 or in the EPCAM gene. If there were to occur a mutation in one of these genes, whose role is of dimers, that would cause the inactivation of the MMR (mismatch repair) system. As a consequence, this would mean the accumulation of mismatched DNA in repeated microsatellite sequences that would eventually lead to carcinogenesis [1,2].

ASSESSMENT

A consequence of the repeated DNA mismatch is the microsatellite instability (MSI). The most common types of cancer in LS are colorectal cancer (CRC) and endometrial cancer (EC).

Known locations for cancer types produced by this syndrome include: ovarian, stomach, pancreatic, urothelial, hepatobiliary tract, small intestine, brain, skin.

Two subtypes of LS II have been recognized:

1. Muir-Torre Syndrome (MTS)

Muir-Torre Syndrome is related to the mutation of the MSH2 gene located on chromosome 2p. It is usually characterized by skin cancer associated with at least 1 visceral malignancy. In addition, in 1967 Muir reported Polyps of the stomach with the basal cell nevus syndrome.

Later on, in 1981 Lynch doubted the nosologic place of the Muir-Torre Syndrome, and in 1984 the MTS would be eventually named "Lynch II".

Nowadays it is categorized a subtype of Lynch II, which associates HNPCC with colorectal cancer only. The genes associated are MLH1 cytogenic location (3p22.2) and MSH2 cytogenic location (2p21-p16) [3,4,8,9].

2. Turcot Syndrome (TS)

Turcot Syndrome is caused by homozygous or compound heterozygous mutation in the mismatch repair (MMR) gene MLH1, located on the cytogenetic region 3p22. Turcot first described it in the year 1959. He presented two siblings a boy and a girl, both having central nervous system tumors and colonic polyps. The boy had a medulloblastoma of the spinal cord and colorectal adenocarcinomas. The girl had glioblastoma multiforme and a pituitary adenoma. It was a consanguineous marriage (third cousins) indicating an autosomal recessive inheritance pattern regarding parents. During the upcoming years, other authors described this syndrome that reported various other types of cancerous tumors and colonic polyps.

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Article History:
Received: 18 April 2022
Accepted: 28 April 2022

TS is a rare autosomal or recessive childhood cancer predisposition syndrome with 4 main tumor types: hematologic malignancies, brain/central nervous system tumors, colorectal tumors and multiple intestinal polyps, and other malignancies including embryonic tumors and rhabdomyosarcoma. The AD form is due to mutations in the MMR genes or in the APC (adenomatous polyposis) gene. The recessive form is due to a biallelic mutation in the MMR genes and is a constitutional mismatch repair deficiency (CMMR-D). It has been observed that in the mutations of the APC gene, the predominant types of cancer are brain cancer and medulloblastomas. In the TS associated with MMR gene mutations the predominant types of cancer are glioblastomas. In the CMMR-D types, the cancer type is usually a hematological malignancy that occurs in early childhood (mean onset of 5.5 years), meanwhile the brain tumors develop a bit later (mean onset of 8 years) [5-7,10].

GENETICS IN LS

The main mutations in Lynch syndrome are presented in Table 1.

TABLE 1. Mutations associated with Lynch syndrome:

Syndrome	Mutation
MMRCS1 - Mismatch repair cancer syndrome 1	MLH1 gene mutation - chromosome 3p22.2
MMRCS2 - Mismatch repair cancer syndrome 2	MSH2 gene mutation - chromosome 2p21-p16
MMRCS3 - Mismatch repair cancer syndrome 3	MSH6 gene mutation - chromosome 2p16
MMRCS4 - Mismatch repair cancer syndrome 4	PMS2 gene mutation - chromosome 7p22

Lynch Syndrome in endometrial cancer

MLH1 related Lynch Syndrome strategies of surveillance according to NCCN:

1) Endometrial cancer can be detected early due to symptoms, therefore women should be properly informed regarding the significance of timely medical evaluation of any uterine haemorrhage or postmenopausal bleeding. The assessment should always include an endometrial biopsy.
2) Total hysterectomy does not reduce the overall mortality but does in fact reduce the incidence of endometrial cancer. Timing of the hysterectomy can be individualized based on childbearing, comorbidities, family history, LS gene variant.
3) Screening for endometrial cancer hasn't shown benefit in women with LS. Endometrial biopsy is precise and sensitive. Screening via endometrial biopsy every 1-2 years starting with the age 30-35 years, can be considered.
4) Transvaginal ultrasound screening for endometrial cancer in postmenopausal women has not been proven to be effective, to be a preferred recommendation. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women as multiple factors can lead to different endometrial stripe thickness during the normal cycle [11].

Risks of developing endometrial cancer in Lynch Syndrome:

PMS2 in LS risk: 16-31% compared to the general population of 3.1%
MLH1 in LS risk: 34-54% compared to the general population of 3.1%
MSH2 and EPCAM in LS risk: 21-57% compared to the general population of 3.1%
MSH6 in LS risk: 16-49% compared to the general population of 3.1% [12-15].

Criteria for the evaluation of Lynch Syndrome:

The main criteria for Lynch syndrome evaluation are presented in Table 2.

TABLE 2. Criteria for Lynch syndrome evaluation:

Known LS pathogenic variant in the family	
Personal history of a tumor with MMR deficiency determined by PCR, NGS or IHC diagnosed at any age	
Any individual with CRC or EC and any of the following	Diagnosed< 50 years of age
	A synchronous or metachronous LS-related cancer regardless of age
	1 first-degree or 2nd-degree relative with LS-related cancer diagnosed
	2 or more 1st- or 2nd-degree relatives with LS-related cancer diagnosed regardless of age
Family history of any of the following	1 or more 1st- or 2nd-degree relatives with a CRC or EC diagnosed <50 years old
	1 or more 1st- or 2nd-degree relatives with a CRC or EC and a synchronous or metachronous LA-related cancer regardless of age
	2 or more 1st- or 2nd-degree relatives with LS-related cancers, including 1 or more diagnosed under the age of 50.
	3 or more 1st- or 2nd-degree relatives with LS-related cancers regardless of age.

Conflict of interest: none declared
Financial support: none declared

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