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INTEGRATIVE REVIEW: PATHOPHYSIOLOGY, DIAGNOSIS, PRESENTATION AND MANAGEMENT OF ADULT PATIENTS WITH LYNCH SYNDROME

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Abstract: Introduction: Lynch syndrome (LS) is an autosomal dominant hereditary disease characterized by increased susceptibility to the appearance of numerous cancers, with the main pathogenic variants related to DNA repair incompatibility, more specifically related to changes in the MLH1 genes, MSH2, MSH6 and PMS2, or deletions of the EPCAM gene. Objective: To clearly explain to the general practitioner how to diagnose and treat LS, aiming to have a positive impact on the underdiagnosis of LS. Methods: Integrative literature review carried out in the databases of PUBMED, Virtual Health Library (VHL), SciELO and LILACS, with the following descriptors "Lynch Syndrome", "diagnosis" and "treatment" and the Boolean "AND". The filters used were "last 5 years" and "free text". Non-relevant articles were excluded, totaling 396, with 28 articles being included in this review. Results: Diagnosis begins with screening tests, which are immunohistochemistry and polymerase chain reaction (PCR), however, confirmation is only with genetic tests. It is recommended to carry out screening and surveillance procedures, treating each neoplasm and functional status of the patient. Conclusion: LS is the most common genetic predisposition for hereditary cancer, but remains underdiagnosed. Therefore, diagnostic knowledge and active search for predisposed family members are essential, as is early intervention.
Keywords: Lynch syndrome; diagnosis; treatment.

INTRODUCTION

Lynch Syndrome (LS) is an autosomal dominant hereditary disease characterized by a variant of the Mismatch Repair (MMR) genes - the four DNA repair genes -, including MLH1 and MSH2 (80%), MSH6 and PMS2 (10- 20%). Also, according to more recent discoveries, by deleting the EPCAM gene, which regulates the expression of MSH2, silencing it. Thus, a germline mutation occurs and, subsequently, a somatic mutation, to inactivate these genes and result in carcinogenesis. (YURGELUN; HAMPEL, 2018) (CINI; QUAIA; CANZONIERI et al., 2019). The alteration of MMR genes occurs essentially in short DNA repeat sequences - microsatellites -, as a result of which errors accumulate, generating microsatellite instability (MI) (WONG; CHRISTIE; GATELY, 2018).

This disease is closely associated with the predisposition to the development of multiple neoplasms, at a systemic level, since each genetic variant is associated with a specific type of cancer (YURGELUN; HAMPEL, 2018). These include colorectal cancer (CRC) and gastric cancer, ovarian cancer, endometrial cancer, small intestine cancer, urothelial cancer (ureter, renal pelvis and bladder), biliary tract, pancreas, breast, prostate, germ cell tumor, mesothelioma, sarcoma soft tissue, skin (melanoma, sebaceous gland adenomas, keratoacanthomas) and brain (glioblastoma) (YURGELUN; HAMPEL, 2018) (SÁ, 2018). In this context, neoplasms in the gastrointestinal tract - duodenum, pancreas, ileum, jejunum and stomach - and ovary have been described resulting from deletions in the EPCAM gene, which is associated with a lower risk of extra-colic neoplasms. The coexistence of Lynch syndrome and benign cutaneous tumors (sebaceous adenomas and keratoacanthomas) characterizes Muir-Torre syndrome, and glioblastomas characterizes Turcot syndrome (MARTINGO, 2021).

Two strategies identify individuals at high risk for the syndrome: clinical criteria and tumor assessment. The Amsterdam I and II criteria and the Bethesda guidelines determine these clinical criteria for Lynch syndrome. Once the Amsterdam criteria or at least one of the Bethesda criteria have been completed, tumor evaluation must be carried out, and regardless of this, genetic tests can also be carried out (STJEPANOVIC; MOREIRA; CARNEIRO et al., 2019).

Currently, two general diagnostic approaches are usually applied to Lynch Syndrome. The first is molecular screening for colorectal cancer and endometrial tumors, to assess MMR function (MMR-D) or identify high levels of MSI (MSI-H), thus identifying patients to be tested for MMR variants. The second is direct germline testing in patients with a suspected family or personal history of Lynch Syndrome. In this sense, individuals with Lynch syndrome can be diagnosed due to a cascade testing process, which was carried out on family members of the patient who had a confirmed diagnosis, or through testing carried out based on a family history of cancer (YURGELUN; HAMPEL, 2018). The methods used are immunohistochemistry (IHC) and microsatellite instability testing, whose agreement is high, as is its sensitivity and specificity (COHEN; PRITCHARD; JARVIK, 2019). In the case of patients with normal IHC without microsatellite instability, the cancer is classified as sporadic, in the case of CRC, Lynch syndrome is excluded. Otherwise, genetic tests are indicated (HAJIRAWALA; BARTON, 2019) and genetic counseling before and after these (MARTINGO, 2021).

Regarding the management of patients with Lynch syndrome, screening and surveillance procedures are recommended based on the neoplasms with which it is associated. For the prevention of colorectal cancer (CRC), since Lynch syndrome is the most common

cause of hereditary colorectal cancer (CCH) and constitutes approximately 3% of all CRC, colonoscopy is indicated. Therefore, annual colonoscopy is recommended from the age of 25 onwards for carriers of MLH1 and MSH2 gene variants, and every two years from the age of 30 onwards for carriers of MSH6 and PMS2 gene variants (DURATURO et al., 2019). Furthermore, prophylactic measures related to ovarian and endometrial cancer from the age of 40 are indicated (YURGELUN; HAMPEL, 2018), such as hysterectomy and/or bilateral salpingo-oophorectomy, which can be discussed for women who have completed their desire to become pregnant or found if in the postmenopausal period (STJEPANOVIC; MOREIRA; CARNEIRO et al., 2019). The pharmacological treatment of Lynch syndrome, to be discussed in this article, includes the use of monoclonal antibodies, which achieve more than 70% control of the disease. Furthermore, according to recent studies, aspirin is being used as a prophylactic medication for Lynch syndrome. (YURGELUN; HAMPEL, 2018).

In this review, an overview of Lynch syndrome will be presented, with its definition, description of the pathophysiology, diagnosis, specific management and prognosis. The established importance of Lynch syndrome is inexorable, as it is closely related to several neoplasms of extreme clinical relevance and severity, in addition to a high incidence in the population. Thus, with the correct diagnosis and management of the syndrome, the patient would have adequate screening for the aforementioned neoplasms and, thus, a structured approach to secondary health care.

MATERIALS AND METHODS

This is an integrative literature review in which a systematic search was carried out in PUBMED and the Virtual Health Library (VHL), which includes the SciELO and LILACS databases, with the following descriptors validated by the Health Science Descriptors (DeCS): "Lynch Syndrome", "diagnosis" and "treatment". The descriptors were exchanged by the Boolean "AND". Articles published in the last 5 years were selected, and in the end, 61 articles were found in the PUBMED database and 360 articles in the VHL, totaling 421 articles.

As inclusion criteria, articles must be complete, in Portuguese or English, from the last 5 years (2017 to 2022), in order to select the most recent articles on the topic. Furthermore, the research must only include adults. Furthermore, the studies could not address specific neoplasms.

Studies that did not answer the research question, incomplete articles and in languages other than Portuguese and English and literary review studies were excluded. Other exclusion criteria were works that addressed specific neoplasms. Additionally, articles containing child participants were also discarded.

The articles found were evaluated independently. Articles duplicated by the Mendeley software duplicate analysis tool were discarded. From this, inclusion and exclusion criteria were established for the evaluation of the selected articles. After careful analysis of the full texts, articles that did not meet the inclusion and exclusion criteria were excluded, leaving 28 articles for the composition of this integrative review.

RESULTS

DEFINITION

Lynch syndrome is one of the most common hereditary cancer syndromes, has a dominant characteristic and is associated with mutations in the germlines of the Mismatch Repair System (MMR) genes – genes associated with DNA repair (LYNCH et al., 2015). Thus, individuals with Lynch Syndrome have a significantly higher chance than the general population of developing colorectal cancer (CRC) and endometrial cancer, as well as cancer of the ovaries, stomach, urothelial tract, small intestine, pancreas, urobiliary tract and skin. (THIBODEAU; SCHAID, 1993)

The syndrome may resemble other clinical conditions also strongly linked to the development of these types of cancer, such as those linked to CRC: FAP (familial adenomatous polyposis) (VACCARO; PERALTA; BONADEO, 2012), and in particular adenomatous polyposis attenuated familial polyposis (AFAP) and recessive polyposis (related to the MYH gene) (NAKAGAWA, 2010).

PATHOPHYSIOLOGY

Lynch syndrome results from a germline mutation of one of the four MMR System genes, MLH1, MSH2, MSH6, and PMS2. Significant deletions in a non-MMR gene, EPCAM – epithelial cell adhesion molecule – have also been linked to the etiology of Lynch Syndrome. (KAUR et al., 2019)

Mismatch repair (MMR) genes play a role in repairing incorrect nucleotide base pairings in the replication of genetic material. If these accidental incompatibilities are not corrected, the resulting copy may not function correctly, leading to a greater chance of developing various types of cancer. (GUPTA; HEINEN, 2019). Furthermore, according to the same author, individuals with this syndrome have a functional allele and a non-functional allele of a specific gene, and due to an inherited mutation, the risk for developing cancer occurs when there is a mutation in the functional allele of this gene., the individual is born with the predisposition but develops the syndrome during life, due to the loss of both alleles and the consequent failure to decode proteins from the specific gene, MMR (SÁ, 2018).

In other words, although mutations in the germlines of the MMR system have an autosomal dominant inheritance pattern, that is, from just one mutated allele, the inactivation of both alleles is necessary for the function of the MMR system to become effective. actually defective. (GUPTA; HEINEN, 2019).

As a general rule, patients with Lynch syndrome have a mutation on one allele of an MMR gene and the other allele is somatically inactivated by mutation, loss of heterozygosity, or epigenetic silencing by hypermethylation. Biallelic inactivation of MMR genes results in a higher rate of mutation in the cell's DNA - genomic instability - due to a failure to repair mismatches - function of the MMR system - a process that normally occurs during normal DNA synthesis. (GUPTA; HEINEN, 2019; TANNERGARD et al., 1995)

Incompatibilities most commonly occur in regions of repeated nucleotide sequences, called microsatellites; Therefore, a characteristic resulting from the loss of effectiveness of the MMR system is the expansion or contraction of microsatellite regions in the tumor, in relation to normal tissue. (TANNERGARD et al., 1995). This genetic alteration is called microsatellite instability (IMS), and is characteristic of tumors associated with Lynch Syndrome. IMS can affect genes that regulate cell growth or apoptosis, or even some of the MMR system genes themselves. The accumulation of mutations in these cancer-related genes

is thought to be the cause of the process of carcinogenesis in individuals affected by Lynch Syndrome. (GUPTA; HEINEN, 2019; TANNERGARD et al., 1995)

By definition, IMS is characterized by the accumulation of small insertion or deletion events in repeated stretches of DNA called microsatellites. When such mutations occur in hotspot microsatellite loci within coding regions of tumor suppressor genes (e.g., TGFBR2), they act to promote carcinogenesis (YURGELUN; HAMPEL, 2018).

However, even today, despite all the existing mechanisms and criteria, there are still large gaps in science for determining and concretely diagnosing Lynch syndrome, as well as regarding its exact genetic pathophysiology, which goes beyond already established studies.

DIAGNOSIS

As previously mentioned, Lynch syndrome is responsible for causing an increase in the predisposition to the development of several types of cancer, the most common being colorectal cancer and endometrial cancer. (DOMINGUEZ-VALENTIN et al., 2020)

Currently, there is data that supports the universal screening of both as a way of identifying people with Lynch Syndrome. (COHEN et al., 2019)

Initially, screening tests are conducted, and if they are positive, suspected individuals are referred to undergo genetic counseling and confirmatory genetic tests. (YURGELUN; HAMPEL, 2018). Two tests can be performed as screening, immunohistochemistry, which allows the analysis of the expression of repair proteins, and PCR, which allows the detection of microsatellite instability in the analyzed tumors. (SVRCEK et al., 2019)

Immunohistochemistry uses antibodies directed against the repair proteins MLH1, MSH2, MSH6 and PMS6, in order to analyze whether there has been a loss in the expression of any of them (SVRCEK et al., 2019). When an absence of expression of any of the tested proteins is identified, the tumor is considered to have MMR, a dysfunction in the DNA repair machinery (YURGELUN; HAMPEL, 2018). This method is fast, cheap and makes it possible to reduce the number of genes analyzed during genetic testing, with an advantage that is currently less relevant with the cost reduction of next generation sequencing. (COHEN et al., 2019)

Microsatellite instability is one of the key characteristics of tumors associated with Lynch syndrome, being present in more than 95% of these tumors (PICÓ et al., 2020). This is characterized as changes in the length of repetitive DNA sequences in tumors in relation to the same loci in non-neoplastic tissue (YURGELUN; HAMPEL, 2018) and can be investigated using the PCR test. The panel considered the gold standard in diagnosis is the Pentaplex panel, which analyzes 5 DNA mononucleotide sequences.

If two or more loci present instability, the tumor is classified as MSI-H, high frequency microsatellite unstable, requiring further investigation. (SVRCEK et al., 2019)

The two screening tests, immunohistochemistry and PCR, have similar sensitivities (PCR - 0.93, IHC - 0.91) and specificities (PCR - 0.79, IHC - 0.83), and the American Association of Gastroenterology does not recommend one technique over another (MENAHEN et al., 2019).

MSI-H or d MMR results, however, are not only present in tumors associated with Lynch syndrome. In reality, most cases of colorectal cancer and endometrial cancer with MSI-H or d MMR develop due to somatic inactivations of gene function, (YURGELUN; HAMPEL, 2018) as in cases of biallelic hypermethylation of the MLH1 gene promoter. (SVRCEK et al., 2019).

Because this is a common change, an additional step is generally performed after PCR, in cases of MSI-H results, or immunohistochemistry, in cases of tumors with deficiency in the expression of MLH1, associated or not with deficiency in the expression of PMS2. (YURGELUN; HAMPEL, 2018; MENAHEN et al., 2019)

At this stage, the tests that can be used are PCR, with direct analysis of the promoter methylation pattern, or, only in cases of colorectal cancer, investigation of the presence of the BRAF V600E somatic mutation (YURGELUN; HAMPEL, 2018; TANAKAYA, 2019).

Among them, direct analysis is the most sensitive and specific test, however, to perform it, DNA must be treated with bisulfite, meaning that this strategy is not immediately available in most hospitals. (YURGELUN; HAMPEL, 2018; SVRCEK et al., 2019)

The last diagnostic step is to carry out genetic testing, since although tumor screening is useful in identifying patients who may have Lynch Syndrome, the definitive diagnosis is only obtained through the identification of a pathogenic germline variant of a Lynch Syndrome gene. repair, obtained by genetic testing (BILLER; SYNGAL; YURGELUN, 2019).

With the drop in the costs of carrying out gene sequencing and the evolution of its performance, changes have been proposed in the diagnosis of the syndrome (COHEN et al., 2019).

A proposed change is the use of next generation sequencing in case screening, with its application in the detection of microsatellite instability, making it possible to use a greater number of loci to determine the instability status (SVRCEK et al., 2019; COHEN et al., 2019;).

The use of multi-gene panels has also been proposed as an alternative to carrying out specific genetic tests. The advantages highlighted are the ability to identify a wide diversity of genes associated with the risk of hereditary cancer (BILLER; SYNGAL; YURGELUN, 2019) and the fact that next generation sequencing has already been used to detect mutations associated with prediction of response to specific therapies in colorectal cancer (SVRCEK et al., 2019). Disadvantages include the potential risk of identifying variants in genes of low or moderate penetrance, which often do not have clear management guidelines, and the detection of genetic variants of undetermined significance (BILLER; SYNGAL; YURGELUN, 2019).

CLINICAL PREDICTION MODELS IN THE DIAGNOSIS OF LYNCH SYNDROME

Clinical prediction models are a way of screening individuals for Lynch Syndrome, when they do not have tumors, but have a family history that raises concern (BILLER; SYNGAL; YURGELUN, 2019).

Traditionally, the clinical criteria adopted were the Amsterdam criteria, created in 1991 and revised in 1999, (tables 1 and 2), and the Bethesda guideline, published in 1997 (table 3) (COHEN et al., 2019; TANAKAYA, 2019).

Screening patients using these clinical criteria, however, does not detect more than a quarter of cases of Lynch Syndrome, and these tests, in practice, have no clinical utility (TANAKAYA, 2019; COHEN et al., 2019).

The PREMM5 predictive model was recently developed, which is the first model to effectively predict the probability of an individual carrying a pathogenic germline variant in one of the 5 genes associated with Lynch Syndrome. PREMM5 calculates this probability based on age, sex and personal and family history of cancer (MANNUCCI et al., 2020). When the test result indicates probability values equal to or greater than

2.5%, genetic evaluation is recommended (BILLER; SYNGAL; YURGELUN, 2019).

All criteria must be present:
1 - Three family members diagnosed with colorectal cancer;
2 - One of these members must be a first-degree relative of the other two;
3 - Members must belong to at least two successive generations;
4 - At least one of the cases must have been diagnosed before the age of 50;
5 - The differential diagnosis of familial adenomatous polyposis must have been excluded;
6 - The tumor diagnosis must have been confirmed in histopathological evaluation.

Table 1 - Amsterdam I Criteria

All criteria must be present:
1 - Three family members diagnosed with cancer associated with Lynch Syndrome (colorectal, endometrial, small intestine, ureter or renal pelvis cancer);
2 - One of these members must be a first-degree relative of the other two;
3 - Members must belong to at least two successive generations;
4 - At least one of the cases must have been diagnosed before the age of 50;
5 - The differential diagnosis of familial adenomatous polyposis must have been excluded;
6 - The tumor diagnosis must have been confirmed in histopathological evaluation.

Table 2 - Amsterdam II Criteria

Tumors from colorectal cancer patients must be tested in the following situations:
1- CRC diagnosed in a patient under 50 years of age;
2- Presence of synchronous or metachronous tumors, colorectal or associated with Lynch Syndrome, regardless of age;
3- CRC diagnosed in a patient under 60 years of age, when he presents histological characteristics of microsatellite instability;
4- CRC diagnosed in a patient with one or more first-degree relatives with tumors associated with Lynch Syndrome, one of which was diagnosed before the age of 50;
5- CRC diagnosed in two or more family members, first or second degree, with tumors associated with Lynch Syndrome, regardless of age.

Table 3 - Bethesda Guidelines

MANAGEMENT

For the adequate management of patients with Lynch syndrome, it is mainly necessary that screening and surveillance procedures for the neoplasms with which it is associated occur. (YURGELUN; HAMPEL, 2018). However, screening guideline recommendations are still limited, with the best-known guidelines being on colorectal, endometrial, and ovarian cancer. (BILLER et al., 2019)

Due to the absence of clinical signs, family history has been the main method for identifying at-risk patients and its implications for the therapeutic management of these patients. Clinical criteria are used to identify suspected families, with Bethesda's being the most widely used. However, there is another section of criteria which is the routine testing criteria: all patients who meet a five percent or greater risk threshold for Lynch syndrome (based on any prediction model) may be appropriate for the test; When tumor testing cannot be performed in a patient suspected of having Lynch syndrome, testing of all four MMR and EpCAM genes simultaneously may be considered; Individuals with an EpCAM mutation must undergo the same surveillance as those with MLH1 and MSH2 mutations; and surveillance recommendations for individuals with MSH6 and PMS2 mutations now include earlier and more frequent colonoscopies. From there, the identified individuals would be subjected to microsatellite instability research and immunohistochemistry in the tumor tissue, in order to identify the missing proteins and thus infer the mutated gene. (EDWARDS; MONAHAN, 2022)

Long-term follow-up of patients has demonstrated that frequent and early colonoscopic evaluation of healthy individuals with Lynch syndrome can significantly reduce the incidence of colorectal cancer, colorectal cancer-associated mortality, and overall mortality, thus solidifying this screening

as the primary way of managing patients with the syndrome. Annual surveillance colonoscopy is recommended from the age of 25. For this to occur, it is necessary to identify carriers of predisposition alleles in patients with any hereditary condition that results in gastrointestinal tumors such as Lynch syndrome, enabling the choice of a more appropriate endoscopic surveillance program and the choice of treatment approach. optimal treatment, resulting in a decrease in mortality due to MMR-associated hereditary colorectal cancer. (DURATURO et al., 2019).

The recent emergence of oncology therapies, based on immune checkpoint inhibitors, which work by manipulating and upregulating patients' own immune systems, has exploited this underlying biology to create revolutionary progress in the treatment of Lynch syndrome, associated with e.g., to the monoclonal antibody pembrolizumab. (YURGELUN; HAMPEL, 2018).

The Food and Drug Administration (FDA) approved pembrolizumab in 2017 for the treatment of tumors with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors, regardless of tumor site or histology., but based on biomarkers. MSI-H tumors share common histopathological features, including neoantigens that can serve as targets for the immune system, making the tumor susceptible to immunotherapy (BATTISTUZZI; PUCCINI; SCIALLERO; 2021).

According to ANDRÉ et al. (2020), Pembrolizumab was shown to be more effective than chemotherapy in cases of MSI-H-dMMR metastatic colorectal cancer, resulting in longer disease progression-free survival. Radiographic response was also better with pembrolizumab, although more patients had progressive disease. Thus, the safety profile of Pembrolizumab was consistent with previous studies, with fewer serious adverse events compared to chemotherapy. These results confirm Pembrolizumab as an initial therapeutic option for the profile of the aforementioned patients.

In this scenario, some studies have observed strong immunological infiltration and an environment rich in cytokines associated with tumors with mismatch repair deficiency because their microenvironment expresses several immune checkpoint molecules, which indicates immune activation counterbalanced by inhibitory signals that resist tumor elimination. These findings suggest that the high mutational burden associated with mismatch repair deficiency is the basis for the greater responsiveness to anti-PD-1 treatment in this subset of genetically defined cancers. Furthermore, changes in the levels of protein biomarkers, such as CEA, have been observed in correlation with the clinical benefit of the treatment (LE et al., 2015). When the anti-PD-1 antibodies pembrolizumab and nivolumab, both in monotherapy, were tested, they achieved lasting results of 31 to 52% in a study of average follow-up time, and in a subsequent study, the combination of the latter with ipilimumab, an anti-PD-1 antibody, -CTLA-4, resulted in greater efficacy, and such a combination was approved by the FDA for restricted treatment for metastatic and dMMR cancer. (SINICROPE; 2018).

In this scenario, it is possible that patients with other DNA repair deficiencies also benefit from treatment with PD-1 inhibitors, such as mutations in POLD, POLE or MYH (LE et al., 2015). However, studies are still needed to prove the use of pembrolizumab over chemotherapy as initial therapy in patients with MSI-H-dMMR colorectal cancer, for example, with the RAS mutation (BATTISTUZZI; PUCCINI; SCIALLERO; 2021). In other words, in most studies, Pembrolizumab is a therapy of choice over

chemotherapy, being a first-line therapy in patients with MSI-H-dMMR colorectal cancer, however, in a subgroup that has not yet been clearly defined, this type of tumor does not show a response. to immune checkpoint inhibitors (GROTHEY, AXEL, 2020).

Therefore, combined therapy strategies have been considered to promote a reduction in the number of patients with disease progression (GROTHEY, AXEL, 2020).

A secondary analysis showed that aspirin and other cyclooxygenase-2 inhibitors work to reduce the risk of colorectal cancer and adenomas based on both observational data and randomized preventive trials, based on an understanding of pharmacogenetic data and the molecular basis of anticancer effects. of aspirin. To investigate whether such cancer prevention benefits apply to patients with Lynch syndrome, the Colorectal Adenoma/Carcinoma Preven on Program 2 (CAPP2) study randomly assigned subjects with Lynch syndrome to receive 600 mg/day aspirin or placebo. A preplanned long-term analysis demonstrated a marked reduction in the incidence of colorectal cancer among participants who took aspirin for 2 or more years compared with those randomly assigned to placebo. There was also a significant reduction in the incidence of any cancer associated with Lynch syndrome among participants, patients who had taken aspirin for 2 years or more, suggesting that the preventive benefits may extend beyond the colorectum. Based on these compelling data, daily aspirin is now considered a standard component of Lynch syndrome cancer prevention. (YURGELUN; CHAN, 2020)

PROGNOSIS

Patients with Lynch syndrome have a 20 to 80% risk of developing colorectal cancer, a 1 to 13% risk of stomach cancer, women have a 15 to 60% risk of endometrial cancer and 1 to 38% risk of ovarian cancer. However, even with this variety of neoplasms associated with Lynch in the literature, colorectal cancer, microsatellite stable tumors and endometrial cancer are recurrent. (DURATURO et al., 2019).

A study done on patients with Lynch syndrome and patients with sporadic colorectal cancer shows that overall colorectal cancer survival in syndromic patients is better than in patients with sporadic CRC. The different outcome is likely related to specific tumorigenesis involving DNA mismatch repair dysfunction. (DURATURO et al., 2019).

Although colorectal cancers associated with Lynch syndrome have superior prognoses compared to their sporadic counterparts, some individuals with Lynch syndrome develop recurrent/metastatic colorectal cancer or other forms of advanced, incurable cancer. (YURGELUN; HAMPEL, 2018). Studies done on Lynch syndrome patients with endometrial cancer and sporadic cases show no difference in outcome. (DURATURO et al., 2019).

Compared with patients who have microsatellite stable (MSS) tumors, those who have MSI tumors are more likely to have local recurrence and peritoneal metastases, with a lower frequency of lung or liver metastases, generally associated with poor prognosis.

Analyzes have demonstrated better prognoses for individuals with MSI/dMMR CRCs compared with pMMR CRCs, particularly in early-stage disease. (ROUDKO et al., 2021)

CONCLUSION

LS is the most common genetic predisposition for hereditary cancer, but it remains underdiagnosed, a fact that can be explained by the lack of knowledge about the existence of this disease, as well as the need for suspicion on the part of the doctor and the performance of genetic tests, which have a high cost in Brazil. Currently, diagnostic methods are increasingly sensitive and specific, increasing the assertiveness index.

In this context, early identification of this disease offers the potential to prevent the incidence of cancer and reduce morbidity and mortality. However, it is worth highlighting that there is significant progress in understanding the risk spectrum of the affected population and in formulating cancer prevention strategies in healthy patients with the aforementioned pathology, including the use of chemotherapy agents and immunological actions.

It is noteworthy that many aspects must be clarified, such as effective treatment, what are the mutations in those patients who do not present any of the known alterations and the timing of screening in individuals with more unusual cancers related to the syndrome. Finally, it is essential to regularly monitor family members of the affected patient, carrying out active searches and early intervention if necessary.

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