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Review Article

A Current View of Lynch Syndrome: The Subdiagnosis and Oncological Recurrence

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Abstract

Lynch Syndrome (LS) is an autosomal dominant heterogeneous genetic disease with incomplete penetrance and with a hereditary Colorectal Cancer (CRC) predisposition factor, being attributed to up to 5% of cases, mainly when observed before the age of 45 [1-3]. Although LS is not the only hereditary syndrome for the development of hereditary cancer, it is the one with the highest incidence. Due to its dominant character, LS presents a 50% probability of passing mutations in DNA repair genes to future generations, which ends up showing the importance of a syndromic diagnosis for early treatment and with minimal systemic changes [3]. The main mutations are in the MLH1, MSH2, MSH6 or PMS2 genes, which are responsible for helping to repair the DNA. This mutation interrupts the correct functioning of these genes and, consequently, accelerates the process of division and proliferation of cells with errors, increasing the risk of the appearance of tumors, corresponding to what we call Microsatellite Instability [4]. The LS can be classified according to its location in: Lynch I and Lynch II. The first classification is the neoplasm present in the colon, while the second classification covers extracolonic neoplasms, the most common being in the endometrium followed by the ovaries, but also possible of being in other places of lower incidence such as stomach, small intestine, hepatobiliary and even genitourinary tract [1,5].

Keywords: Colorectal Neoplasia, Classification, Lynch Syndrome, Primary Prevention.

Objective

The objective of this work is to make a review about the Lynch Syndrome with a present point of view, clarifying the importance of knowing this disease. In addition, to make patients aware of Colorectal Cancer in people at family risk, in order to ensure survival for these patients through early diagnosis.

Method

This is a bibliographic review performed in the databases of the Virtual Health Library (VHL) and Scientific Electronic Library Online (SciELO). We used as inclusion criteria, articles published between the years of 2018 to 2020. A full text filter was used, among them conducted in Portuguese, Spanish and English.

Literature Review

Previously known as Hereditary Non-polypous Colorectal Cancer, the Lynch Syndrome is an autosomal dominant heterogeneous genetic disease that occurs due to germline mutations in DNA repair genes. These mutations alter the normal function of these genes, and consequently accelerate the process of cell division and multiplication of cells with errors, increasing the risk of the appearance of tumors [1,4,6]. The main genes affected are MLH1, MSH2, MSH6 or PMS2 [4]. LS is the most common form of hereditary Colorectal Cancer in the world and its prevalence in the general population is about 1 in 500 [5,6]. This syndrome can

be classified into two types, according to its location. Lynch I is when the disease affects the colon, while Lynch II is an extracolonic disease [5]. Lynch II is the main form of cancer manifestation affecting the endometrium, ovary, breast, small intestine, stomach, ureter, bile duct, pancreas, prostate, brain, renal pelvis, among others [1,5,6].

Despite being hereditary, some factors may be associated with the early diagnosis of Colorectal Cancer in people at risk for Lynch Syndrome, such as unhealthy habits, consumption of processed foods, red meat, alcohol, smoking and obesity [3]. For the diagnosis of LS, some methods can be counted on, however, prevention and awareness strategies about the risk of the disease have lower costs and equally efficient benefits [3]. The main point to be worked on is the awareness of patients, as there is still little knowledge about risk factors, signs and symptoms of LS [2].

Discussion

Lynch Syndrome is part of one of the syndromes that increase the susceptibility to the development of more common malignancies that should be investigated in patients with cancer before the age of 45 [3]. This syndrome has a very complex mechanism for the development of cancer, which basically comes down to the instability of microsatellites in which it allows the accumulation of mutations that end up modifying that genetic material and allowing autonomous and irreversible clonal proliferation, what corresponds to cancer [7]. In the face of current research, there has been an increase in the diagnosis of LS due to conditions in which first-degree relatives have had clinical manifestations associated with Colorectal Cancer and also with the endometrium and ovary, but even so it remains an underdiagnosed syndrome with a need of greater evidence in the scientific field, mainly for the establishment of an active surveillance of family members aiming an early viewing of these lesions, which would present a much more favorable prognosis according to the course of the disease [7].

When we think of Lynch Syndrome type I - the one that predisposes to Colorectal Cancer - some anatomopathological criteria are essential for its description. Macroscopically, it is showed as vegetating masses with a hardened and friable aspect and a preference for the proximal colon, which, according to their anatomy, weakens an early diagnosis even more. In addition, tumor masses tend to be synchronous, in other words, multiple tumor masses are distributed within the large intestine, which is why colonoscopy with biopsy is performed, being the preferred guideline for its diagnosis. Still, due to its location being preferably by the proximal colon, mainly at the level of the cecum, it is worth remembering that this structure has an extremely broad light and a thinner wall than the rest of the colon due to the presence of liquid excreta, therefore the manifestations clinics tend to be later, which gives the patient a more reserved prognosis.

The most common clinical manifestations in these patients are fever of unknown origin, presence of a palpable mass at the level of the right iliac fossa, iron deficiency anemia associated with tumor hemorrhage since they are quite friable masses and significant weight loss without an apparent cause in a short period of time. [8]. Microscopically, the lesions present themselves as adenocarcinomas, malign neoplasms of the glandular epithelium, of undifferentiated aspect. In other words, the neoplastic tissue is totally different from the epithelial tissue of a normal colon, presenting a high mitotic activity and consequently a worse prognosis, being these tumors highly aggressive, presenting the appearance of signet ring cells in some of them. In others, diagnosis based on histopathology is impossible, requiring the use of immunohistochemistry to confirm or complement the tumor phenotype to establish a more appropriate treatment [8].

Besides that, hereditary cancer not associated with adenomatous polyposis describes an earlier metastasis, mainly for the liver and peritoneum, which are the main locations, in which the manifestations may vary from painful hepatomegaly or not (depending on the frequency of distention of Glisson's capsule), even cases of ascites that vary according to the volume measurement. In cases associated with endometrial cancer, moderate to large metrorrhagia has been observed, often associated with pelvic discomfort, other signs and symptoms may also be associated with tumor metastasis. Finally, when we think of ovarian cancer associated with this syndrome, there is a tendency to bilaterality with voluminous masses that tend to trigger mainly gastrointestinal and genitourinary symptoms due to the anatomy of the location, and tend to be heterogeneous masses associated or not with necrosis that make early metastasis for the peritoneum which culminates in cases of massive ascites, in addition to abdominal discomfort and the above-mentioned symptoms, such pathophysiology contributes significantly to the onset of dyspnea due to difficulty in diaphragmatic movement and also constipation due to ascitic fluid compressing the intestine and even the stomach [9].

Final Considerations

Nowadays, medical improvement in the diagnosis of genetic syndromes is increasingly necessary for the most varied causes, mainly neoplastic alterations, in which its early diagnosis can be an important step in the lives of these patients. Like any other malignancy, mutations in the DNA of repair genes allow the accumulation of mutations that leads to the development of these lesions. Although there is no cure, scientific knowledge about Lynch Syndrome is extremely necessary for the active surveillance of the patient and family members, especially those of the first degree, in which they should be informed about the early need for screening tests, mainly regarding colonoscopy after 25 years. Therefore, in the face of the suspicion of LS, an extensive family investigation

should be carried out, which can motivate genetic tests through blood and saliva in which they aim to diagnose LS early, without forgetting an investigation of the ovaries and endometrium by means of transvaginal ultrasonography with Doppler fluxometry and endometrial hysteroscopy with biopsy, if necessary. For parents who had Colorectal Cancer before the age of 40 and mothers who also have endometrial and early ovarian cancer, suspicion should be raised, and the condition should be conducted in the best possible way, always precluding investigation.

Like any other malignant pathology, a detailed anamnesis should be instituted for family information, in search for both the origin and frequency of cancer in the family (mainly those associated with Lynch Syndrome type I and type II) and the patient's syndromic condition, or that is, its signs and symptoms that guide this pathology, always remembering the importance of valuing any patient's complaint, as this makes a total difference for the most appropriate conduct to be applied. All of this complemented by a complete physical examination, with a thorough evaluation of the abdomen and pelvis, palpation of the main drainage lymph node chains, whether local or more distal, such as supraclavicular lymph nodes, in addition to the general physical examination in which the patient is evaluated as a whole, not forgetting the importance of vaginal touch, rectal touch, among other diagnostic modalities for the diagnostic approach of tumor lesions. The treatment for both situations is quite varied, depending on the tumor stage and can vary from a colectomy with intestinal transit reconstruction to radiotherapy and chemotherapy. For endometrium, ovary and other places of lesser incidence, the same criteria apply.

However, we must remember that all cases of Colorectal Cancer should be tested for Lynch Syndrome, globally eliminating this titration of syndromic underdiagnosis and mainly offering family members a suitable follow-up to prevent the worsening of such condition, since such syndrome is associated with aggressive forms of cancer which lead the patient to an early death, and that is why active family surveillance is necessary to avoid this situation. Facing the current scenario, the diagnosis is made by the patient's family and individual history, immunohistochemistry tests, genetic tests of BRAF and analysis of MSI - the last two of which are associated with the great question of the present regarding prophylactic surgery. Given this, it is totally valid to say that studies on the repair genes associated with Lynch Syndrome are essential to gain research with valuable data for modern science in which it would impact on improving the lives of patients and everyone around them, including health professionals who are in close relationship with the family.

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