Hereditary Colorectal Cancer: The Importance of Recognition as a Preventive Measure

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Abstract

Hereditary colorectal cancer (CCH) is a pathology related to inherited genetic alterations that predisposes to the development of neoplasia (colorectal, gastrointestinal, gynaecological, and others) in young patients. The simple recognition of the syndrome is fundamental for the accomplishment of the tracing of the relatives and the prevention of the cancer in these individuals. The objective of the present study was to carry out a bibliographic review, as well to present the profile of suspected clinical cases identified in the department of General Surgery of the Gaffrée and Guinle University Hospital in a period of thirteen months, addressing aspects related to diagnosis and treatment.

Keywords: Lynch syndrome, Profile, Screening

Introduction

Colorectal cancer (CCR), the most common malignant neoplasm of the digestive tract, has increased its incidence, especially in developing countries, which are considered low-risk areas.[1] In Brazil, according to the National Cancer Institute (INCA), the estimated number for 2014/2015 is approximately 576,000 new cases of cancer in Brazil, of which 33,000 are colon and rectum.

Approximately 80% of patients develop colorectal cancer sporadically, and in 20% there is genetic susceptibility involved.[1] Among inherited forms, non-polyposis hereditary colorectal cancer (CCNHP) is the most common, responsible for 3% to 5% of all colorectal cancers.[2]

Non-polyposis hereditary colorectal cancer (CCHNP), commonly referred to as Lynch syndrome, is an autosomal dominant disease predisposing to neoplasms, with 80% penetration, due to germ line mutation in one of the DNA repair genes (mismatch repair-MMR) -*hMLH1*, *hMSH2, hMSH6* and *PMS24*.[3] The syndrome is characterized by increased susceptibility to colorectal cancer (Lynch Syndrome 1) and other extracolonic tumors such as ovarian, endometrial, breast, gastric, pancreatic, ureteral and renal pelvis.

Genetic bases

Lynch syndrome, as previously mentioned, is an autosomal dominant disease caused by mutations in the DNA base pair repair genes belonging to the class MMR (mismatch repair). The initial identification of the genetic basis of the syndrome began in the 1990s from the location of the *hMLH1* and *hMLH26* genes. Since then, four *MMR* genes have been clearly linked to the development of the disease: *hMLH1* (chromosome 3p21-3), *hMSH2* (2p22-p21), *hMSH6* (2p16) and *hPMS2* (7p22).[3,7] Combined, mutations in the

hMHL1 and hMHS2 genes account for 80-90% of the disease cases, while mutations in the *hMSH6* genes contribute to 10%, and in the *hPMS2* gene to about 5%.[4]

Most of the mutations observed in *MMR* genes are frame shift or nonsense, resulting in truncated protein products.[8] Traditional analysis techniques may fail to identify other mutations of loss of function: missense mutations occur 30% of the time, particularly in the *hMLH1* and *hMSH6* genes, and may cause functional deficiencies that are not detected by immunohistochemistry.[8,9] Thus, more sophisticated methods of analysis may be needed to identify the full spectrum of mutations.

Defects in the *MMR* genes lead to the characteristic findings of microsatellite instability (MSI), commonly identified by the five key test for microsatellite replication errors.[4,10] Changes in the microsatellite sequences lead to mutations of genes that act on the regulation of cell growth. The gene encoding TGF-β (growth-transforming factor β) contains a microsatellite susceptible to mutation in case of MSI. Mutations in this gene inactivate the TGF-β receptor, which inhibits the growth of normal intestinal epithelial cells. MSI also determines mutations in the *BAX* gene, which is an important promoter of cellular apoptosis, accelerating the adenoma-carcinoma sequence.[3,11]

High frequency microsatellite instability-MSI-H (high) characterized by two or more mutated microsatellite sequences, is detected in more than 90% of the colorectal tumors of Lynch syndrome. Conversely, the absence of protein products from MMR genes in immunohistochemistry has a predictive value close to 100% for MSI-H.[12] High frequency microsatellite instability is also identified in 15 to 20% of sporadic RCCs. In most cases, the findings result from hyper methylation of the *hMLH1* gene promoter caused by mutations in the *BRAF* gene.[13]

Specific genetic defects are recognized as predisposing to different phenotypic expressions. Mutations in the hMSH2 gene are associated with the Muir-Torres phenotype variant, in which CCHNP is accompanied by multiple cutaneous sebaceous adenomas, sebaceous carcinomas and keratoacanthomas.[10] Mutations in the *hMHL1* and *hPMS2* gene may be linked to Turcot's syndrome, an association of CCHNP with brain tumors.[14] Mutations in hMSH6 are involved with higher rates of endometrial cancer, but with lower rates of CRC. Homozygosity for hMLH1 and hMSH2 or composite heterozygosity may produce atypical abnormalities, such as haematological malignancies and neurofibromatosis.[4]

The clinical presentation is heterogeneous, but the syndrome is usually characterized by colorectal cancer with an early age (mean age 45 years), with predominance of lesions located in the right colon, 70% of which are located near the hepatic flexure, with an increased number of synchronic and metachronous tumors. There is a predominance of mucinous and poorly differentiated adenocarcinomas, as well as a single spectrum of benign and malignant extra-colonic tumours.[7,15] Endometrial cancer occurs in 43%, gastric cancer in 19%, urinary tract cancer in 18% and ovarian cancer in 9% of affected individuals. Extracolonial neoplasms are more prevalent in women, since in them the risk of developing endometrial cancer is greater than the risk of developing colorectal cancer. The cumulative risk of developing any neoplasia at age 70 is approximately 90% in men and 70% in women affected.[4]

Two syndromes were initially described. Lynch I syndrome, characterized by colon cancer in relatively young individuals, and Lynch II syndrome, characterized by families at risk of colorectal and extracolonic cancer, such as ovarian, endometrial, gastric, pancreatic, ureteric and pelvic cancers renal.[16]

The diagnosis of Lynch syndrome requires the investigation of a precise and detailed family history, as well as knowledge of the disease and its characteristics by the

physician, who may be facing the first case within a family. However, it is important to recognize that although the family history of colorectal cancer helps when present, its absence does not exclude Lynch syndrome.[15]

Family history has been the main way of identifying patients at risk of developing the syndrome, since there are no clinical signs or symptoms that are capable of predicting such susceptibility. The International Collaborative Group (ICG) created the 1990 Amsterdam criteria for susceptible families to be identified. Because they are highly restrictive, the Amsterdam criteria have been expanded, including other tumors related to Lynch syndrome (colorectal, endometrial, small intestine, gastric, pancreatic, ureteral and renal pelvis), giving rise to the modified Amsterdam criteria.[3]

The introduction of the Bethesda criteria, created in 1997 by the American National Cancer Institute (NCI), during a consensus conference, and subsequently revised, led to further liberalization in the identification of these patients. The Bethesda criteria were established to identify individuals and families in whom Lynch syndrome is suspected and for whom testing for microsatellite instability would be indicated. It was proposed at the conference that five microsatellite markers for detection of MSI in Lynch Syndrome: BAT25, BAT26, D5S346, D2S123 and D17S250 were screened.[4,16] In 2002, the original criteria were revised and expanded, and in 2004, they were revised again, including the findings of the Muir-Torres syndrome. Although the sensitivity of the Bethesda criteria is greater than that of the Amsterdam criteria, they both present weaknesses in sensitivity and specificity for disease diagnosis.[17]

It is important to keep in mind that not all individuals with Lynch Syndrome will meet these criteria. Therefore, the doctor must have a high index of clinical suspicion to diagnose the disease. It is equally important to recognize that only about 60% of families meeting the Amsterdam criteria have inherited anomalies in an *MMR15* gene. The term "family type X colorectal cancer" has been suggested to distinguish families that fully meet the Amsterdam criteria but have no evidence of a defect in the *MMR* gene, since relatives in these families appear to have a lower incidence of colorectal cancer than those belonging to families in which a mutation in the *MMR* gene was identified. In addition, about 20% of newly discovered cases of Lynch Syndrome are caused by spontaneous mutations in the germ lineages, so that family history sometimes does not reflect the genetic character of the syndrome.[4]

With the identification of defects in *MMR* genes as the main underlying cause of the syndrome, it is clear that traditional and genetic criteria do not completely overlap.[4] Some algorithms for the screening of Lynch syndrome have been tested using quantitative models based on clinical parameters. Wijnen et al. created a statistical model through logistic regression capable of predicting the possibility of diagnosis of Lynch syndrome based on the following variables: mean age of CRC diagnosis, presence of the Amsterdam criteria, number of relatives with CRC, number of relatives with endometrial cancer, presence of patients with other neoplasms associated with the syndrome, and patients with multiple synchronic or methaconic tumors. Lipton et al. developed a model similar to that of Wijnen, revealing good sensitivity and specificity in the diagnosis of the disease.[3]

Although there is no consensus in the literature regarding the screening of patients with Lynch syndrome, some steps can be followed to identify these patients. Clinical criteria should be used first, with Bethesda being the most widely used.[3] The identified individuals would then be submitted to microsatellite instability research and to the immunohistochemical analysis of the tumor tissue, identifying the missing proteins and, consequently, loss of expression of the mutated gene. Testing of *MMR* genes for Lynch syndrome may reveal variants of uncertain significance or cases of incomplete or

variable penetrance, which require careful counselling.[4,7] In families whose tumor tissue is not available, testing of the initial germ line can be considered. The third step (gold standard) would be genetic sequencing.[1]

Materials and Methods

This is a retrospective study based on the review of medical records of patients with suspected Lynch Syndrome diagnosed with a surgical service at the Universitry Hospital Gaffrée e Guinle (HUGG). These patients (index cases) were identified using modified Bethesda clinical criteria. From the identification of the index case, first-degree relatives were screened through upper digestive endoscopy, colonoscopy, trans vaginal ultrasonography, and mammography.

The following variables were analyzed: age at diagnosis of cancer, sex, tumor location, histological type of tumor, site of family tumors, presence of synchronic or metachronous tumors, family history of cancer related to the syndrome, and family tracing findings. These data were used to trace the profile of patients with suspected Lynch's syndrome treated at HUGG.

Results

Fourteen index cases were identified, involving a total of 71 patients evaluated directly in the outpatient clinic of General Surgery. The youngest patient was 23 years old at the time of diagnosis.

As to the tumor location, of these index cases (14), 12 colorectal tumors and 2 gastric tumors were found.

Among the cases of colorectal tumors, 7 of them were located in the right colon, 4 in the left colon and 1 in the rectum. There were 2 cases of metachronous tumor (thyroid and adrenal).

In a period of 13 months, 33 colonoscopies, 28 endoscopies of the upper digestive tract, 11 mammograms and 19 transvaginal ultrasounds were requested, as well as other specific exams that varied according to the individual clinical history.

In these examinations we found: 01 transverse colon tumor and 14 individuals with polypoid lesions (1 adenocarcinoma) to colonoscopy; 01 polyp of endometrium and 01 ovary cyst to trans-vaginal ultrasonography; 01 gastric polyp to upper digestive endoscopy.

The department procedures in this period included: 01 catheter implant for chemotherapy, 01 left video endoscopic colostomy, 01 videolaparoscopic right adrenalectomy, 01 hepatic segmentectomy (V), 04 right hemicolectomies, 04 left colectomies, and 01 total hysterectomy abdominal resection with voluminous ovary cyst. Totalizing 13 surgical procedures performed in 13 months of clinical investigation.

Treatment

The treatment of Lynch syndrome remains a controversial subject. It is known, however, that intensive surveillance with annual colonoscopy and polypectomy can minimize the incidence of colorectal tumors. Nevertheless, even with annual colonoscopic examinations, there is still a risk of cancer developing in the interval between exams, but the appearance of the tumor during the colonoscopic surveillance program is related to more favorable stages of the disease, with greater therapeutic possibilities.

The treatment plan is based on dividing patients into three groups: patients with confirmed Lynch syndrome who have CCR; patients with confirmed but non-cancerous Lynch syndrome and patients at risk for the syndrome but who are not able to perform the genetic test of predisposition.

Patients with CCR with a confirmed diagnosis of HNPCC should be treated by total colectomy with ileoretal anastomosis due to the high incidence of methachronic CCR (more than 40% in 10 years).[5] In addition, these patients should undergo endoscopy of the rectal stump remaining due to the high risk of cancer. In cases not yet operated on, in which there is a rectal tumor without the presence of a colonic tumor, a total proctocolectomy can be performed with ileo-anal anastomosis and ileal pouch confection.

In the group composed of patients known to have inherited genetic defect but no cancer, there is controversy as to whether or not total prophylactic colectomy with ileocostal anastomosis is performed. Since the mutated gene's penetrance is about 80%, some patients would undergo surgery without need. There is a tendency to not perform prophylactic surgery, the most accepted course being strict follow-up with colonoscopy every 1 to 2 years (from the age of 20 to 25 years) and annually for those over 40 years, in addition to upper digestive endoscopy and abdominal and pelvic imaging tests. Given the increased evidence for acceleration of the adenoma-carcinoma sequence in Lynch Syndrome, annual colonoscopy should be strongly considered. For women, annual vacuum endometrial aspiration with onset around the age of 30 years, as well as transvaginal ultrasonography and determination of CA-125 levels is also recommended. [1,4] In the case of a postmenopausal female patient or with no desire to become pregnant again, prophylaxis through total abdominal hysterectomy with bilateral salpingo-oophorectomy may be offered, but still without scientific evidence of its efficacy. Finally, ultrasound and urinary cytology every 1 or 2 years is recommended for screening for malignant changes in the urinary tract.

The group of patients who cannot perform the genetic test should be subdivided into patients with and without cancer. For those without cancer who do not know whether or not they have inherited genetic defect, prophylactic surgeries should not be indicated, but strict follow-up with periodic examinations, as if they had Lynch's syndrome. On the other hand, those diagnosed with cancer should be treated individually according to the site of the injury.[3,4]

The diagnosis of Lynch Syndrome initially depends on clinical suspicion on the part of physicians. Considering the high cost involved in performing genetic testing[6] (besides the impossibility of its execution in most Brazilian public hospitals,[7] both for economic or structural reasons), the identification of families with Lynch syndrome and the knowledge of the profile of these patients, based on clinical criteria, may provide important data for the national literature, since they will contribute to the increase of the diagnosis in our country and may serve as an initial step for future research at the molecular level.

Discussion

The profile of patients with a strong suspicion of having Lynch's Syndrome treated in the Service of Surgery A of the Hospital Universitário Gaffrée and Guinle seems to have similarities with the available records regarding the disease, considering the parameters evaluated. The mean age at diagnosis of the first tumor (40,45 years) observed in our sample was very close to that found in the literature (about 45 years). In addition, the location of the lesions, with predominance of tumors in the right colon, is in agreement with the data of the literature. In the study, of the 12 colorectal cancer samples, 3 of them

were classified as adenocarcinoma with little differentiation and only 1 as mucinous carcinoma, but the reduced number of cases index of the sample prevents further inferences regarding this parameter.

The detection of polyps in 14 colonoscopies makes the importance of screening even more evident, since in Lynch Syndrome there is a faster progression to malignant lesions due to the acceleration of the adenoma-carcinoma sequence. Screening by colonoscopy allows the endoscopic resection of these polyps, thus reducing the chances of developing colorectal malignancy. There were also two cases of tumor recurrence, after a period of only one year, detected through colonoscopic surveillance, showing the importance of follow-up with annual colonoscopy for patients with Lynch Syndrome.

The profile of our patients shows the lack of knowledge of a large number of medical professionals regarding Lynch's syndrome since a good part of the patients presented clinical criteria compatible with the syndrome (mean age at the diagnosis of 40,45 years and family history of cancer present in most cases) and, even so, no family members were tracked. A simple family history obtained through a quality anamnesis is an important diagnostic tool for Lynch syndrome, as family history is the initial step in the identification of individuals at risk of developing neoplasms associated with the syndrome.[18] Clinical suspicion on the part of the physician becomes even more relevant as genetic testing remains a distant reality in the vast majority of Brazilian public hospitals. The clinical suspicion can be made only on the basis of simple knowledge of the existence of the disease, and no technological apparatus is necessary. Knowledge about the disease can save the lives of many people, since screening family members can prevent the development of cancer or lead to its diagnosis in earlier stages of the disease.

It is also clear the importance of clarifying patients about the disease, since they end up acting as a link between possible new cases in the family and hospital care, enabling the detection of tumors in stages with greater chances of success in treatment. Many family members, probably because they are unaware of the risks and severity of the disease, have refused to participate in the screening, which involves simpler and less costly procedures than the treatment of tumors that may be diagnosed at later stages of the disease. The cultural level may contribute to the low index of adherence of family members to participate in the tracking program, even though the benefits are explained. Despite our active search, large numbers of family members refuse to trace. The knowledge of this characteristic profile of our population should be used to adopt measures that result in a greater adherence of this population to the tracing.

In summary, data from the present study indicate that we are faced with a large problem, since most medical professionals are not aware of this disease and, as a result, diagnosis is usually late and relatives are not screened . In addition, there is clear difficulty convincing all family members to participate in the tracking program. Thus, recognition of the profile of patients with suspected Lynch Syndrome in our country will contribute greatly to the adoption of measures that reverse this reality. Among them, continued medical education, the formation of multidisciplinary team in the management of these patients and the implementation of public policies of screening for populations at high risk.

Conclusion

The results were compatible with the literature, emphasizing the importance of the diagnosis of the patients with the syndrome and the tracing of the relatives. Knowledge of the profile of these patients will allow the implementation of public screening policies for populations at high risk of developing hereditary colorectal cancer, in addition to

providing benefits for these patients, since the objective is to make an early diagnosis and, consequently, to provide a greater perspective of healing and better quality of life.

This simple knowledge has the power to save lives, as it is able to prevent the development of cancer in a young population.

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