

Identification of patients at-risk for Lynch syndrome in a hospital-based colorectal surgery clinic

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Abstract

AIM: To determine the prevalence of a family history suggestive of Lynch syndrome (LS) among patients with colorectal cancer (CRC) followed in a coloproctology outpatient clinic in Southern Brazil.

METHODS: A consecutive sample of patients with CRC were interviewed regarding personal and family histories of cancer. Clinical data and pathology features of the tumor were obtained from chart review.

RESULTS: Of the 212 CRC patients recruited, 61 (29%) reported a family history of CRC, 45 (21.2%) were diagnosed under age 50 years and 11 (5.2%) had more than one primary CRC. Family histories consistent with Amsterdam and revised Bethesda criteria for LS were identified in 22 (10.4%) and 100 (47.2%) patients, respectively. Twenty percent of the colorectal tumors had features of the high microsatellite instability phenotype, which was associated with younger age at CRC diagnosis and with Bethesda criteria ($P < 0.001$). Only

5.3% of the patients above age 50 years had been previously submitted for CRC screening and only 4% of patients with suspected LS were referred for genetic risk assessment.

CONCLUSION: A significant proportion of patients with CRC were at high risk for LS. Education and training of health care professionals are essential to ensure proper management.

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Key words: Colorectal cancer; Family history; Hereditary cancer; Lynch syndrome; Microsatellite instability phenotype

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INTRODUCTION

Family history of colorectal cancer (CRC) is a clinically significant risk factor and may be reported by up to 15% of all patients with the disease. Lynch syndrome (LS, OMIM: # 120435), also called hereditary non-polyposis colorectal cancer syndrome (HNPCC), is the most common inherited colon cancer predisposition syndrome. It is an autosomal dominant syndrome caused by germline mutations in the mismatch repair (MMR) genes *hMLH1*, *hMSH2*, *hMSH6* and *PMS2*. The syndrome accounts for 2%-3% of all CRC diagnoses and for 5%-9% of the diagnoses of endometrial cancer in patients under age 50 years^[1-4]. Other extra-colonic tumors including ovarian, upper urologic tract, gastric, small bowel, biliary/pancreatic and brain cancers have been described at an increased frequency in families with LS^[5]. The cumulative lifetime risk of cancer varies depending on geographic/environmental factors and the age-related incidence of each tumor type^[6-8]. Furthermore, the cancer spectrum in families affected with the syndrome varies significantly based upon the DNA MMR gene mutated and the specific mutation^[9,10].

Determining the prevalence of LS among patients with CRC is an important public health issue. Affected patients have an increased risk for second primary cancers and their identification can lead to specific screening and intervention recommendations for patients and their at-risk relatives^[11-13].

Cancer family history is an important tool to identify at-risk patients and families. The Amsterdam criteria, ini-

tially including only CRC and later all tumors of the LS cancer spectrum, define clinical diagnosis of LS and are in themselves an indication for MMR mutation testing. However, even the revised Amsterdam II criteria have a relatively low sensitivity (< 80%) which has turned out to be a major limitation for LS diagnosis. More recently, the Bethesda guidelines were developed to identify a larger proportion of MMR mutation carriers (Table 1)^[14].

Multiple other strategies for identifying individuals with LS have been proposed, including predictive mathematical models to define prior probabilities of carrying a germline MMR mutation, family history instruments and routine testing of CRCs from patients with specific risk factors (e.g. age < 50 years), but the effectiveness of these approaches continues to be debated and has limited applicability in clinical practice^[9,10].

In this study, we aimed to determine the prevalence of a family history suggestive of LS among patients with CRC followed in a coloproctology outpatient clinic of a University Hospital in Southern Brazil, and to identify all potential LS patients who should be referred for genetic counseling. Also, we investigated the frequency of tumors with histopathologic features suggestive of microsatellite instability (MSI) and whether screening recommendations were correctly modified according to the risk identified.

MATERIALS AND METHODS

Ethics

This study was approved at the Institutional Ethics Committee (GPPG-HCPA) under the number 05-257.

Patients

All consecutive patients with a diagnosis of CRC who had an appointment in the outpatient Coloproctology clinic of Hospital de Clínicas de Porto Alegre (HCPA), in Porto Alegre, Southern Brazil, from December 2005 to December 2006, were considered for participation in this study. From a total of 250 patients seen in this period, 212 unrelated patients with adenocarcinoma of the colon and rectum and without a previous diagnosis of inflammatory bowel disease were invited and agreed to participate in the study. After signature of informed consent forms, data regarding personal and family cancer history, pathology reports and additional relevant clinical and/or surgical information were collected. Information collected included types of cancer and age at diagnosis, presence of multiple (synchronous or metachronous) tumors, type and periodicity of colorectal screening, tumor histology, clinical and histological stage of tumors (Dukes and TNM Staging System), family history of cancer (first, second and third degree). Tumor diagnoses in family members were confirmed by medical records and/or death certificates whenever possible.

“Early-onset” colorectal or endometrial cancer was defined as cancer diagnosed before the age of 50 years. All other extra-colonic tumors described in the LS (ovarian, upper urologic tract, gastric, small bowel, biliary/pancre-

Table 1 Clinical criteria for Lynch syndrome

Name	Criteria	Sensitivity ¹	Specificity ¹
Amsterdam	Amsterdam criteria I	61.0%	67.0%
	Three or more relatives with colorectal cancer, one of whom is a first-degree relative of the other two; FAP should be excluded		
	Colorectal cancer involving at least two generations		
	One or more colorectal cancer cases diagnosed before the age of 50		
	Amsterdam criteria II	78.0%	61.0%
	Three or more relatives with histologically verified LS-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), 1 of whom is a first-degree relative of the other 2; FAP should be excluded		
	Colorectal cancer involving at least two generations		
	One or more cancer cases diagnosed before the age of 50		
Revised Bethesda	At least one of the following features	90.9%	77.1%
	Bethesda 1: Colorectal cancer diagnosed in a patient under the age of 50		
	Bethesda 2: Presence of synchronous or metachronous colorectal cancer, or other LS-associated tumors ² , regardless of age		
	Bethesda 3: Colorectal cancer with the MSI-H histology ³ under the age of 60		
	Bethesda 4: Colorectal cancer in one or more first-degree relatives with an LS-related tumor, with one of the cancers under the age of 50		
	Bethesda 5: Colorectal cancer in two or more first- or second-degree relatives with LS-related tumors, regardless of age		

¹Data on sensitivity and specificity of Amsterdam criteria from Syngal *et al.*^[14] and Revised Bethesda from Piñol *et al.*^[46]; ²Lynch syndrome (LS)-associated tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel; ³Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern. FAP: Familial adenomatous polyposis; MSI-H: Microsatellite instability-high.

atic and brain) were considered in the pedigree analyses^[5]. Colorectal surveillance was considered appropriate when colonoscopy was performed by or after age 50 years in patients with no history of CRC in first- or second-degree relatives, and in those with a positive family history, when performed 10 years before the earliest diagnosis of CRC in the family, and every 1-2 years thereafter.

The criteria used to identify patients with LS or at-risk for the syndrome included the Amsterdam I and/or II criteria for clinical diagnosis^[5,15] and the Bethesda Revised Criteria^[16] for a potential diagnosis.

Statistical analysis

SPSS version 16.0 was used for data handling and statistical analyses. For descriptive analysis, categorical variables were described by their absolute and/or relative frequencies and quantitative variables were expressed as mean \pm SD. For analytical statistics, the existence of an association between categorical variables was examined using χ^2 . The Student's *t* test was used to determine the significance between different ages at diagnoses among two independent groups. A difference with a *P* value of less than 0.05 was considered significant.

RESULTS

Clinical information on the 212 patients studied is summarized in Table 2. Mean age of the patients at recruitment was 62.33 years (range: 24-99 years, SD = 12.8 years), and 113 (53.3%) were female. Of the 212 patients, 45 (21.2%) were diagnosed with CRC under the age of 50 years and the mean age at first CRC diagnosis was 59.8 years (range: 20-99 years, SD = 13.1 years). Approximately

Table 2 Sample description by criteria for Lynch syndrome (*n* = 212)

Lynch syndrome criteria	<i>n</i> (%)
Amsterdam	22 (10.4)
Amsterdam I	16 (7.6)
Amsterdam II	6 (2.8)
Bethesda (at least 1 of the 5 criteria)	100 (47.2)
Bethesda (2 or more of the criteria)	41 (19.3)
Bethesda by criteria	
Bethesda 1	45 (21.2)
Bethesda 2	17 (8.0)
Bethesda 3	27 (12.7)
Bethesda 4	23 (10.8)
Bethesda 5	36 (17.0)

5.2% of the patients had a synchronous or metachronous colorectal tumor (*n* = 11) and the mean age at diagnosis in this group was 51.6 years (range: 36-80 years, SD = 13.1 years), lower than the mean age in patients without metachronous colorectal tumor (59.3 years, range: 20-99 years, SD = 12.8 years), as expected (*P* = 0.051). Two patients (0.9% of the sample) were diagnosed with familial adenomatous polyposis.

The age at diagnosis of the first cancer varied from 20 to 86 years (mean = 58.9 years; median = 59 years; SD = 12.9 years). A second primary cancer was present in 33 patients: CRC in 11 (33.3%), endometrial in 2 (6.1%), breast in 2 (6.1%), prostate in 6 (18.2%). The age at diagnosis of the second primary varied from 39 to 99 years (mean = 66.5 years, SD = 13.2 years). One patient was diagnosed with four different primary tumors: two colon cancers at ages 36 and 55 years, endometrial can-

Table 3 Features of the 223 colorectal tumors in the 212 probands¹

Feature	n (%)
Tumor site	
Ascending colon	22 (9.9)
Transverse colon	12 (5.4)
Descending colon	11 (5.0)
Rectosigmoid	158 (71.1)
Other (cecum, unspecified site)	19 (8.6)
Total	222 (100.0)
Missing data	1
Differentiation	
Well differentiated	20 (10.0)
Moderately differentiated	157 (78.1)
Poorly differentiated	24 (11.9)
Total	201 (100.0)
Missing data	22
Mucinous feature	15 (6.7)
Total	223 (100.0)
Missing data	0
MSI-high phenotype ²	42 (21.3)
Total	197 (100.0)
Missing data	26
Dukes stage (n = 195)	
A	6 (3.1)
B	76 (39.0)
C	87 (44.6)
D	26 (13.3)
Total	195 (100.0)
Missing data	28

¹Cases with missing data were excluded from the analysis; ²Cases included all patients with microsatellite instability-high phenotype, independent of age.

cer at 45 years, bladder cancer at 61 years and renal carcinoma at 62 years; all of them confirmed with pathology records. This patient was later found to carry a germline mutation in *hMLH1* (data not shown).

Among the 212 unrelated probands, family history of cancer up to second-degree relatives was observed in 60.4% of patients with early-onset and 52.4% of those with late-onset CRC diagnoses. Twenty-nine percent of the patients reported a family history of CRC and almost 50% fulfilled criteria for LS: 22 (10.4%) fulfilled Amsterdam I and/or II criteria and 100 (47.2%), Revised Bethesda Criteria. In the families of probands with LS criteria, 180 relatives had cancer and the most frequent primary sites were: colon and rectum (43.4%), lung (8.9%), breast (7.8%), stomach (6.7%), endometrium (6.7%), ovaries (3.9%) and prostate (3.4%). As expected, this distribution was different in patients without LS criteria: colon and rectum (30.8%), lung (12.3%), breast (12.3%), stomach (4.6%), uterus (1.5%), ovarian (0%) and prostate (12.3%). About 2.5% of the patients had relatives with multiple primary tumors: one case was diagnosed with uterine and ovarian cancer, and another with colorectal, esophageal and gastric cancer.

Family history of breast cancer was present in 6.4% of the sample with available information (11/171). Among the patients with at least one of the Bethesda criteria, 12% had a family history of breast cancer, compared to 7.1% among patients with none of the criteria ($P = 0.248$).

Table 4 Comparison of different features among patients with and without the microsatellite instability-high phenotype (n = 197¹) n (%)

Features	MSI-high phenotype (n = 42)	Non MSI-high phenotype (n = 155)	P
Age at diagnosis < 50 yr	18 (42.9)	29 (18.7)	0.001
Family history of colorectal cancer	15 (35.7)	45 (29.0)	0.404
Presence of Revised Bethesda criteria ^[16]	42 (100)	56 (36.1)	< 0.001
Presence of Amsterdam II criteria	6 (14.3)	15 (9.7)	0.391
Second primary tumors	3 (7.1)	8 (5.2)	0.620
Early stage at diagnosis	11 (26.2)	64 (41.3)	0.079

¹15 patients were excluded due to missing data on tumor histology. MSI: Microsatellite instability.

In the overall sample, 22 (9.9%) patients had a tumor in the ascending colon and 21.3% had colorectal tumors with histology suggestive of MSI-high (MSI-H) phenotype (Table 3). The clinical features of patients with and without this phenotype are shown in Table 4. As expected, MSI-H histological features were more commonly seen in patients with CRC diagnosed at a younger age (18 patients from a total of 42, $P = 0.001$) and in patients who fulfilled the Bethesda criteria (in all 42 patients, $P < 0.001$). Opposite to what was expected, in a significant number of tumors from individuals fulfilling Amsterdam criteria, histological features suggestive of MSI-H phenotype were not encountered.

Of the 212 charts reviewed, 17% had the family history previously documented. Furthermore, when the previously documented family histories were compared to the pedigrees obtained during patient interview for this study, there was concordance of data in only 56.6% of cases. On the other hand, of the 100 patients with a family history of cancer and fulfilling Bethesda criteria for LS, 57.0% had their family history previously collected and/or reported in the chart by clinicians or surgeons, but a clinical suspicion of LS was not documented in the chart in any of these cases. Only 4% of the patients with clinical criteria for LS were referred for genetic cancer risk evaluation.

Finally, 5.3% of patients with indications for population-based screening by colonoscopy starting at age 50 years had been submitted at least once for colonoscopy before the diagnosis of CRC. Among the 100 patients at risk for LS, only 4.1% had been offered surveillance colonoscopy previously.

DISCUSSION

As in most familial cancer syndromes, early age of onset and multiplicity of cancers have been considered hallmarks of LS. In registry-based series, the mean age at first CRC is about 45 years, compared to 65 years for sporadic CRC, and some LS patients present with CRC in their twenties. Similarly, the mean age of endometrial cancer is about 50 years, which is about 10 years younger than the average age of sporadic endometrial cancer.

As our knowledge of the influences of genetics on cancer risk has increased, so has the need to improve physicians' awareness of the importance of familial cancer history and its proper recording in the medical chart^[17]. Although there is no consensus about the correct method for obtaining information on cancer family history, and using it as a screening tool^[18], general practitioners usually collect the family history data at the time of registration^[19] and different groups have reported screening the adult population for increased genetic risk of cancer using postal questionnaires^[20,21]. Unfortunately, however, health professionals in the first line of patient contact are usually unaware of how and when to contact genetic services. Many specialists, especially coloproctologists and gastroenterologists, have a key role in identifying high-risk patients; the ability to suspect a patient to be at risk for a cancer predisposition syndrome is crucial for a rapid diagnosis and to ensure appropriate care.

Nearly 30% of patients in our study reported a positive family history of CRC, which is much higher than observed positive CRC family history in the general population: approximately 9.0%^[22]. Our findings also indicate that the hereditary CRC phenotype can be easily identified in outpatient coloproctology units, using a systematic approach after proper training of the staff, as reported previously^[20,21].

Surprisingly, a high number of patients fulfilling Amsterdam criteria were found in our sample (22/212, 10.4%), significantly higher than previously reported in the Brazilian population. Viana *et al.*^[23], reviewing 311 medical records of CRC patients from São Paulo, Brazil, found a frequency of 1.3% in families with Amsterdam criteria. The reason for such a high incidence remains to be explained. One potential limitation of this study is the fact that the outpatient coloproctology clinic from which the patients derive is located in a tertiary care university hospital, and reference center for many diseases in the region. Thus, a higher percentage of high-risk patients, including those at risk for hereditary cancer may exist in this setting than in other general hospitals.

An additional point to consider is the fact that this institution has, since 2001, one of the few cancer risk evaluation clinics in Southern Brazil. This fact, however, would ideally be associated with high indices of correct identification and referrals of the hereditary cases, which was not observed in most cases. Most patients evaluated in our study did not have an accurate family history assessment in their charts, (description of family history was present in the charts of only 57.0% of potential LS patients). Moreover, only 4% of patients with LS criteria were referred for genetic counseling, suggesting that even when detailed family cancer history is obtained, it may not be granted the necessary importance. Previous investigations have already reported significant gaps in the documentation of family cancer history in medical charts. Analyzing data from the Direct Observation of Primary Care study, Medalie *et al.*^[24] found that only 40% of 2333 audited charts documented the presence or absence of a family history of breast or colon cancer. Even when family cancer history is obtained, its interpretation seems to

be problematic as referrals often focus on rarer, hereditary cancer syndromes, neglecting cases of average and moderate risk individuals. Tyler and Snyder found a similar deficiency in the referral process among family physicians: from 10 patients considered at moderate or high risk, only 3 had been identified and none had been referred for cancer genetic consultation^[25].

Also, although previous studies have shown a clear benefit for surveillance colonoscopy in patients with suspected or proven LS^[26,27], in our series it was not common practice. Several factors could be contributing to this observation: patient's refusal, physician omission of adequate familial risk assessment and or referral and/or limited access to screening examinations. Our results are in agreement with those previous studies, considering that only 5% of the patients evaluated were undergoing proper screening. The identification of high-risk precursor lesions is considered critically important and colonoscopy screening for individuals with LS is recommended to begin at age 25 years, or 10 years younger than the earliest diagnosis of CRC in the family, whichever comes first, every 1-2 years^[28].

Multiplicity of cancers is a hallmark of LS and according to the literature about 10% of identified Lynch patients have more than one cancer by the time of diagnosis. Although CRC is the most common, other frequent findings include cancers of endometrium, ovary, stomach, small bowel, pancreas, hepatobiliary system, renal pelvis, ureter and glioblastoma. Approximately 20%-40% of patients have been reported to develop metachronous CRC after initial resection if a subtotal colectomy is not performed^[29]. Similarly, clustering of more than one Lynch-associated cancer (colorectal and uterine) in an individual patient should raise suspicion of LS. In our population, among all CRC cases, approximately 15% of patients had a second primary cancer. The most common second primary was CRC (metachronous or synchronous), endometrium, breast and prostate.

The most common extra-colonic tumor in LS is endometrial carcinoma, which develops in up to 70% of women who are mutation gene carriers^[30]. Thus, the presence of endometrial cancer in the family history of an individual with CRC, a feature encountered in 12 (6.7%) of the patients studied here, should always raise a suspicion of LS. When the endometrial cancer is diagnosed under the age of 50 years, the probability of LS is particularly high. This has been confirmed by a high rate of MMR deficiency (up to 40%) in women with early-onset endometrial cancer^[31,32]. Consistent with this, the National Comprehensive Cancer Network (NCCN) has recently revised its guidelines and currently recommends annual surveillance of the endometrium for LS families, as well as MMR deficiency investigation for all women diagnosed with endometrial cancer under age 50 years^[28].

There is some debate with regard to whether prostate or breast cancers might be part of the LS, since some studies have found a high frequency of such tumors among HNPCC families^[33,34]. Oliveira Ferreira *et al.*^[22] found a 26.5% frequency of breast cancer in families fulfilling Amsterdam criteria from São Paulo, Southeastern

Brazil, a higher rate than found in general population-based studies, which could suggest existence of a subset of mutations in this region that are also associated with a higher breast cancer risk. In our study, we found breast cancer at a frequency of approximately 9% in families fulfilling Amsterdam criteria. Although it is common to see LS pedigrees with breast cancer, most genetic and immunohistochemical studies on familial breast cancers have not found any strong relationship with the MMR system deficiency^[35,36]. Recently, a case report of a Lebanese family with LS found a *MSH2* gene defect in a breast cancer tumor of early-onset, suggesting that it could be involved in accelerated breast carcinogenesis^[37]. However, more studies are needed to define such association.

Different studies have shown that CRC in LS differs from typical sporadic CRCs in location, histology, and natural history. Also, it usually displays findings that are suggestive of MSI, such as intense lymphocytic infiltrates, extensive areas with poorly differentiated tissue and mucinous histology^[38]. Overall, 20.3% of the tumors evaluated in this series demonstrated one or more histological features suggestive of MSI-H, similar to previous studies^[39]. In the last few years, it has been suggested that histology could be useful in selecting CRC patients for molecular testing for LS^[40-43], since limiting testing to patients with MSI-H histology could reduce the burden of molecular testing by 60% compared with testing all patients who meet the Revised Bethesda Criteria. More importantly, it could help identify LS among patients with late onset and no cancer family history^[39].

Interestingly, among patients who fulfilled the Amsterdam criteria, only 28.6% presented tumors with features of MSI-H phenotype. This is somewhat surprising and could indicate that in this group of patients, the strong family history of CRC may not be related to abnormalities in the MMR system, and that there could be an increased prevalence of what has been called in the literature the Familial Colorectal Cancer Type X^[44]. Recently, Abdel-Rahman *et al*^[45] analyzed the molecular features of the tumors in CRC patients with MMR germline mutations and in sporadic CRC. They concluded that tumors from the MMR gene-negative group exhibited a novel molecular pattern characterized by a paucity of changes in the common pathways to CRC, which could be associated with non MSI-H histology. Molecular studies with this population are now being carried out in order to test such hypothesis.

Large population-based studies have shown that a family history of CRC in first-degree relatives is associated with an increased risk of CRC. In this study we have shown that a significant proportion of patients diagnosed with CRC and followed in an outpatient clinic of a university hospital in Southern Brazil have either a significant family history of cancer or pathology features suggestive of LS. Our findings underscore the importance of adequate familial risk assessment and, also, of considering MSI-H pathology features in the identification of at-risk patients. Education and training of physicians is essential to ensure that hereditary cancer patients and families are identified and properly referred for genetic counseling and

long-term cancer screening programs. The reason for the high prevalence of patients at risk for LS in our population requires further investigation.

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COMMENTS

Background

The incidence of colorectal cancer (CRC) is currently rising in Southern Brazil. Patients at-risk for the hereditary forms of the disease are diagnosed at younger ages, and have an increased risk for second colorectal tumors and extra-colonic malignancies. Identification of these patients can lead to specific screening and intervention recommendations.

Research frontiers

In this study, the authors describe high prevalence of patients at-risk for Lynch syndrome (LS) in a coloproctology clinic and results support the principle that education and training of health care professionals are essential to ensure proper management of these individuals.

Innovations and breakthroughs

The study draws attention to the high frequency of potential LS patients in a coloproctology clinic in Southern Brazil. It reinforces the importance of correct identification of these cases and suggests further investigations of the origins for these observations.

Applications

Description of the high frequency of hereditary CRC cases in this setting is the first step to demonstrate that adequate familial risk assessment is fundamental to identify at-risk patients.

Peer review

Study was undertaken very well. It's a well written paper. It highlights the importance of identifying high risk groups in order to carry on with surveillance in CRC.

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