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Incidence and Clinical Characteristics of Colonic and Extra Colonic Lynch Syndrome Manifestations in Uruguayan Mismatch Repair Carriers

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Abstract

Background: Colon cancer is a frequent diagnosis worldwide affecting both men and women. Lynch syndrome in an autosomal dominant inheritable condition, accountable for 5 to 7% of colon cancer, as well as other malignancies.

Methodology: From a Uruguayan high risk cancer clinical setting, adult probands from 115 families, registered between 2015 and 2016, meeting Amsterdam I, II or Bethesda Revised guidelines, were tested for MMR genes and EPCAM.

Results: Pathogenic Lynch Syndrome mutations were detected in 23.4% families. A total of 90 mutation carriers were diagnosed, from which information regarding molecular diagnosis, cancer diagnosis, cancer site, tumor staging, age at diagnosis and course of treatment was carefully analyzed. Cancer diagnosis before determination of carrier status was seen in 52.5% individuals; were 46.8% had more than one cancer diagnosis throughout lifetime, mostly colon cancer. The average age for colon cancer was 36.9 years old and 77% were stage II at diagnosis. Consequently, surgical treatment was the most frequent option, and partial colectomies the preferred surgical choice.

Conclusions: Young age of onset and metachronous tumors are part of Lynch syndrome hallmark. How effective surveillance strategies are, are reflected on how well and timely we identify these young high risk adults. Treatment options are most frequently surgical ones, because of the stage these malignant tumors are found upon diagnosis. There is no unanimous consensus about the best surgical strategy for colon cancer Lynch syndrome carriers.

Keywords: Lynch syndrome; Colon cancer; Amsterdam I and II criteria; Revised Bethesda Guidelines; Partial colectomy

Introduction

Colon cancer (CC) is a frequent topographic site for oncological patients worldwide. Accounting for 1800 newly diagnosed Uruguayans per year, being the second most common cancer in women and the third in men [1]. Estimations regarding hereditary colon and endometrial cancer (EC) predisposition, situates Lynch Syndrome (LS) as the main responsible with a 5- 7% and 3% prevalence respectively [2]. Mutations identified in the mismatch repair genes (MMRg) and EPCAM, are behind LS molecular diagnosis [3]. Inherited in an autosomal dominant manner within the families.

Maximum risk for developing such malignancies before 70 years of age, for a LS mutation carrier, versus general population cancer risk, are estimated by the National Comprehensive Cancer Network [4] to be of: 82% vs 5.5% for CC; 60% vs 2.7% for EC; 13% vs <1% for gastric cancer; 24% vs <1% for ovarian cancer; 4% vs <1% for hepatobiliary tract; 7% vs <1% for urinary tract; 6% vs <1% for small bowel; 3% vs <1% for brain and 6% vs <1% for pancreatic cancer.

Clinical suspicion for LS is raised when meeting the Amsterdam I, Amsterdam II, or Revised Bethesda Guidelines **(Table 1)**. Since one in every 35 CC are due to LS [5], emphasis is made on identifying carriers, because of different treatment options and preventive specific measures that should be taken, oriented towards a positive impact in morbidity and mortality of mostly young high risk adults.

Methodology

A total of 115 colon cancer high risk probands (meeting Amsterdam I, II, and Revised Bethesda guidelines) were registered in a two year period (2015-2016) and offered genetic cancer risk assessment, in a genetic counselling clinical setting. Alive, consenting, colon cancer adult probands were tested for MMR genes and EPCAM: MLH1, MSH2, MSH6, PMS2, using Next Generation Sequencing, and Multiplex Ligation Dependent Probe Amplification (MLPA). Positive test results were confirmed by Sanger sequencing. Adults family members were invited for Sanger sequencing to stablish their carrier status. Confirmed LS mutation carriers were included in

this review. Information regarding molecular diagnosis, cancer diagnosis, cancer site, tumor staging categorized according to the American Joint Committee on Cancer (AJCC), age at diagnosis and course of treatment was carefully analyzed.

Table 1 Amsterdam I, Amsterdam II and Revised Bethesda Guidelines for suspecting LS.

Amsterdam I	At least 3 relatives with colon cancer with all of the following:
	1 affected person is a first degree relative of the other two affected persons 2 successive generations affected At least 1 case of colon cancer before age 50 Exclusive of familial adenomatous polyposis
Amsterdam II	Same as Amsterdam I, but admitting other Lynch syndrome related tumors:
	Endometrial, ovarian, rectal, gastric, small bowel, pancreatic, brain, hepatobiliary and urinary tract
	Two cases of Lynch syndrome related tumors in one person, including synchronous and metachronous cancer, regardless of age. Colon cancer and a degree relative (or more) diagnosed with a Lynch syndrome related tumor (one of them diagnosed before 50 years of age). Colon cancer diagnosed before 50 years old. Colon cancer with MSI-H histology diagnosed younger than 60 years of age. Colon cancer diagnosed in a diagnosed in a patient with two or more first-or-second-degree relatives with LS-related cancers regardless of age.

Results

From the 115 Amsterdam I, II and Revised Bethesda guidelines candidates, 27/115 were molecularly diagnosed as LS patients (23.4%) as a result of pathogenic mutations. Positive rates related to clinical features were as follows: 70.4% corresponded to Amsterdam II; 14.8% to Amsterdam I and Bethesda Guidelines respectively.

From those 27 probands, 16 were positive for MLH1, 8 for MSH2, 2 for MSH6 and 1 for PMS2.

When analyzing a total of 213 relatives by Sanger sequencing, 90 tested positive as SL carriers (42.3%). Almost equally divided by gender: 46 women and 44 men. Regarding LS MMR genes there were 55 MLH1 carriers; 26 MSH2 carriers; 8 MSH6 carriers; and 1 PMS2 carrier.

When considering cancer diagnosis, from 90 LS mutation carriers, 47 displayed cancer before determination of carrier status (52.5%). Where 22/47 (46.8%) had more than one cancer diagnosis through lifetime: colon cancer and extra colonic cancer 13/22; synchronic or metachronous colon cancer 5/22; extra colon cancer only 4/22. Those LS mutation carriers with only one cancer diagnosis 24/47 (51.0%), were divided into two subgroups: 16/24 displaying colorectal cancer; and 8/24 with extra colonic manifestations only. One patient was tested because of personal history of 11 adenomatous polyps and concordant family history for LS. Synchronic colon cancer was confirmed in 4 patients.

The most common cancer diagnosis for the 47 patients were: right sided colon cancer 66% (31/47); left sided colon cancer 34% (16/47); endometrial cancer 12,7% (6/47); rectal cancer 10.6% (5/47); urologic cancer 10,6% (5/47) (ureteral, bladder and prostate cancer); transverse colon cancer 8.5% (4/47); gastric 6,4% (3/47); small intestine 4.2% (2/47); ovary 2.1% (1/47); keratocantoma 4.2% (2/47), cervical 2,1% (1/47) and glioblastoma 2.1% (1/47).

Considering colon cancer only, the average age for first CC diagnosis was of 36.90 years old (ranging from 20 to 53 years). The 8 mutation carriers with a second colon primary or metachronous tumor, were diagnosed 10 years after with an average age of 46.8 years old (ranging from 36 to 56 years). The 4 patients that had a third colon cancer were diagnosed 18 years from their first diagnosis. Almost all patients with synchronous or/and metachronous tumors were MLH1 carriers, with 2 exceptions being MSH2 carriers **(Table 2)**.

Table 2 LS mutation carriers diagnosed with polyps or cancer, stratified by site, ICD-10, age at diagnosis, stage and type of surgery.

#	Identification Number	LS Gene	Cancer/Polyps site	ICD 10	Age Diagnosis	Age first CC	Age second CC	Age third CC	Stage (*In situ*)	Surgery
1	5981_88896	MSH2	Left colon+right colon, urether	18,66	29,64	29 Synchronic			Unavailable,3	Left hemicolectomy, total colectomy, no surgery

2	5981_823712	MLH1	Left colon+ right colon, urether	18, 18,66	39,54,53	39	54		3,2, Unavailable	Left hemicolectomy, total colectomy, nefrectomy and partial urether resection
3	5981_823714	MLH1	Left colon	18	43	43			2	Left hemicolectomy
4	5981_80024	MLH1	Jejunum	17	52				2	Segmental resection
5	5981_80025	MLH1	Right colon	18	41	41			2	Total colectomy
6	5981_82981	MLH1	Right colon	18	50	50			2	Total colectomy
7	5981_82982	MLH1	Right colon, endometrium	18,54	27,60	27			2, Unavailable	Right hemicolectomy, histerectomy+bilateral ooforectomy
8	5981_829859	MLH1	Right colon, rectum	18,20	50,65	50			Unavailable	Parcial colon resection, total colectomy
9	5981_829873	MLH1	Right colon	18	23	23			Unavailable	No surgery
10	5981_83011	MLH1	Right colon +transvse colon	18	36	36 synchronic			2	Right hemicolectomy
11	5981_80015	MSH2	Cervix	53	48				Unavailable	Histerectomy
12	5981_800117	MSH2	Rectum	20	52				2	Anterior rectal resection
13	5981_800121	MSH2	Ovarian, rectum	56,20	38,48				3,2	Anterior rectal resection, hysterectomy +bilateral ooforectomy
14	5981_800128	MSH2	Right colon	18,66,67	30,50,51	30			3, Unavailable, *In situ*	Right hemicolectomy, nefrectomy, endoscopic resection
15	5981_800129	MSH2		70	41				4	No surgery
16	5981_408215	MLH1	Right colon	18, 18, 18	20,41,56	20	41	56	4,2,2	Right hemicolectomy, parcial colon resection, total colectomy
17	5981_408216	MLH1		18,54	40,47	40			Unavailable, 4	Right hemicolectomy, hysterectomy+bilateral ophorectomy
18	5981_408219	MLH1	Right colon	18, 18, 18,61	33,51,54,72	33	52	54	Unavailable	Right hemicolectomy, segmental colectomy, total colectomy
19	5981_408220	MLH1	Right colon	18, 18,44, 18	33,38,40,53	33	38	53	2,4,2,2	Right hemicolectomy, parcial resection, skin tumor resection, total colectomy
20	5981_408225	MLH1	Left colon	18,44	38,40	38			Unavailable	Left hemicolectomy, skin tumor resection
21	5981_408226	MLH1	Right colon	18,20	36,42	36			1, *In situ*	Right hemicolectomy, endoscopic polipectomy
22	5981_408227	MLH1	Right colon	18,54	40,44	40			2, *In situ*	Right hemicolectomy, hysterectomy+bilateral ooforectomy
23	5981_408223	MLH1	Right colon	18	37	37			2	Right hemicolectomy

24	5981_408234	MLH1	Duodenum	17	38				2	Partial duodenal resection
25	5981_278	MLH1	Sigmoid, cecum	18, 18	32,36	32	36		3,4	Sigmoidectomy, no surgery
26	5981_831746	MLH1	Left colon, right colon	18, 18	46,56	46	56		Unavailable, 2	Left hemicolectomy, total colectomy
27	5981_849910	MLH1	Gastric	16	54				3	Sub total gastrectomy
28	5981_849918	MLH1	Right colon	18	33	33			2	Right hemicolectomy
29	5981_840911	MLH1	Right colon	18	31	31			2	Right hemicolectomy
30	5981_871814	MLH1	Right colon	18	24	24			3	Right hemicolectomy
31	5981_811714	MLH1	Breast, transvers colon + sigmoid	50, 18, 18	39,35	35 synchronic			2, *in situ*, 2	Tumorectomy, total colectomy
32	5981_85906	MLH1	Endometrium	54	53				Unavailable	Histerectomy+bilateral oophorectomy
33	5981_85909	MLH1	Right colon	18	47	47			4	Total colectomy, histerectomy +bilateral oophorectomy
34	5981_806430	MSH2	Gastric	16	58				1	Sub total gastrectomy
35	5981_806432	MSH2	Sigmoid colon	18	48	48			2	Sigmoidectomy
36	5981_806433	MSH2	Right colon, left colon	18, 18	36,42	36	42		2, *In situ*	Right hemicolectomy, endoscopic resection
37	5981_806435	MSH2	Right colon	18	32	32			3	Right hemicolectomy
38	5981_806436	MSH2	Right colon	18	34	34			3	Right hemicolectomy
39	5981_806437	MSH2	Right colon	18	42	42				
40	5981_86554	MLH6	Endometrium, breast	54,50	47,61				3	Histerectomy+bilateral oopforectomy, cuadrantectomy
41	5981_865517	MLH6	Endometrium, right colon	54, 18	39,38	38			2,2	Right hemicolectomy, histerectomy+bilateral ooforectomy
42	5981_90737	MSH2	Right colon	18	53	53			2	Right hemicolectomy
43	5981_907931	PMS2	11 Colonic adenomas, no cancer							Polipectomy
44	5981_84221	MLH1	Right colon, transverse colon	18	28	28 Synchronic			2	Total Colectomy
45	5981_84751	MSH2	Sigmoid	18	32	32			3	Sigmoidectomy
46	5981_83391	MLH1	Breast, right colon, gastric	50,18,16	45,51,62	51			2,2,4	Tumorectomy, right hemicolectomy, no surgery
47	5981_86041	MLH1	Right colon	18	34	34			3	Right hemicolectomy

48	5981_91411	MLH1	Left colon	18	25	25	56	56	3	Left hemicolectomy

When associating colon cancer stage at diagnosis, all colon cancer tumors were considered (first tumors, new primaries, with or without extra colonic manifestations). Analyzing all 47 CC diagnosis, 39 tumor definitive stages were gathered, were 77% were stage II; 26% stage III; 5% stage I and 5% stage IV **(Table 2)**.

Treatment wise, the vast majority was treated with surgery as expected for stage II CC. Diverse surgical options were observed even for the same tumor topography. Five different categories were made: partial resections or hemicolectomies only 65.7% (23/35); partial resections or hemicolectomies with endoscopic resection for second primary 2.9% (1/35) when second primary was an *in situ*-tumor (all polyp-derived) and passible of total endoscopic resection; partial resection or hemicolectomy ending in total colectomy when second primary was diagnosed 20% (7/35), with 3 total colectomies done after a third tumor diagnosis; total colectomies for a first colon diagnosis in 11.4% (4/35) **(Table 2)**.

When contemplating extra colonic tumors, the average age at diagnosis was of 51.8 years old for rectal cancer; 45 years old for small intestine; 58 years old for gastric cancer; 59.5 years old for urologic tumors; 48.3 years old for endometrial cancer; keratocantoma at 40 years old; glioblastoma at 41 years old; and ovarian cancer at 38 years old **(Table 2)**.

Endometrial cancer and ovarian cancer were treated as a single entity, performing hysterectomy and bilateral salpingooforectomy in all cases. From 6 women diagnosed endometrial cancer, 4 also had a CC diagnosis **(Table 2)**.

After determination of mutation status, surveillance was suggested for all LS mutation carriers, according to posttest genetic counselling corresponding protocol:

Colonoscopy every 12 to 18 months, starting at 20 or 25 years old, depending on the age of the youngest CC diagnosis in the family. Perform polypectomy whenever possible regardless of polyp size. Daily aspirin 100 mg intake. If CC is diagnosed, consider total colectomy vs partial colectomy. According to both patient and physician opinion. Upper endoscopy every 2 years, starting at 35 years old, only when family history of gastric cancer. Transvaginal ultrasound every year, starting at 35 years old. Consider bilateral salpingo-ophorectomy and/or hysterectomy when completing childbearing. According to both patient and physician opinion. Urinalysis and urinary tract ultrasound every year, starting at 30-35 years old.

Discussion

Estimations propose a not negligible cipher of 1 out of 440 individuals carrying a LS mutation worldwide. A vast variety of tumors are implied, were colon and endometrial cancer occupy the top of the list, with 50%–80% risk for colon cancer and 40%–60% for endometrial cancer respectively [6]. Patients and/or families arising clinical suspicion for LS is the first step of many towards molecular diagnosis. Amsterdam I, II and Revised Bethesda guidelines are the cornerstone for which LS patients are identify [7,8]. Nevertheless, the sensitivity of this criteria is only 40 to 80 percent according to current literature [9,10]. Active surveillance modalities, such as periodic colonoscopies with associated polypectomy (if necessary); gynecological screening; adequate and opportune surgeries, are considered effective prophylactic/preventive measures for mutation carriers. The ultimate goal is to prevent death and assure when possible a high life quality in spite of cancer genetic predisposition [6,11,12].

Colon cancer incidence is described as similar for both MLH1 and MSH2 mutation carriers (84% and 71%). MSH2-mutation carriers show a higher incidence (48–61%) of extra colonic malignancies (gastric, pancreatic, small bowel, rectal, urological and ovarian cancer) when compared to MLH-mutation carriers (11–42%) [13]. MLH1 and MSH2 mutation carriers have an overall higher cancer risk (44–79% and 38–78%) when compared with MSH6 and PMS2 mutation carriers; and the highest cumulative risk for CC at age 70 (50–65% and 40–65%, respectively), with a mean age of onset of 43–46 years old [14].

There are similar surveillance strategies for LS patients regarding colonic and extra colonic tumors prevention. There is consensus about effectiveness of prophylactic surgery for gynecologic malignancies. There is not a unanimous surgical strategy for LS colon cancer victims. Prophylactic colectomies are not usually recommended, because of inherent surgical mobility and mortality. Metachronous CC is a hallmark for LS patients despite regular endoscopic screening. It doesn't differ by gender, or mutated gene, it is also independent from the clinic or pathological characteristics of the first colon cancer, or the patient's age at time of surgery [15].

A study estimated the risk of metachronous CC for 382 gene mutation carriers (172 MLH1, 167 MSH2, 23 MSH6 and 20 PMS2) from the Colon Cancer Family Registry [15], who had surgery for their first colon cancer, using retrospective cohort analysis. None of 50 subjects who had extensive colectomy was diagnosed with metachronous CC (incidence rate 0.0; 95% CI 0.0 to 7.2 per 1000 person-years). Cumulative risk of metachronous CC was 16% (95% CI 10% to 25%) at 10 years, 41% (95% CI 30% to 52%) at 20 years and 62% (95% CI 50% to 77%) at 30 years after segmental colectomy. Risk for metachronous CRC was diminished 31% (95% CI 12% to 46%; p=0.002) for every 10 cm of bowel removed.

Performing extended colon resections is sometimes recommended, but not always. According to the last version of the National Comprehensive Cancer Network of 2016, CC management is contemplated with colonoscopy starting at age 20–25 or 2–5 years prior to the earliest colon cancer if it is diagnosed before age 25, and repeat every 1–2 years [4]. Guidelines from a European Group of Experts [12] regarding

the substantial risk of a second CC after partial colectomy (considering similar quality of life after partial vs subtotal colectomy), strongly suggests the option of subtotal colectomy. Also, pros and cons should be discussed with all patients, especially younger CC patients.

Conclusion

Lynch syndrome is the most common cause of CC and EC worldwide. Genetic testing is historically offered to families meeting Amsterdam I, II or Revised Bethesda Guidelines criteria. In a two-year period, 115 probands meeting testing criteria were studied. Molecular diagnosis was obtained in almost a quarter of tested cases, due to low clinical criteria sensitivity, achieving a shy 23.5%. When diagnosis was reached, MLH1 and MLH2 shown to be the most common MMR genes involved compared with MSH6 and PMS2 mutation carriers (24/27 vs 3/27), as already expected. CC was diagnosed at young ages (36.9 years old), in right topographies and in stage II tumors, which is consisting for LS patients.

The preferred surgical strategy for almost all cases 89% (31/35), were conservative colon resections: hemicolectomies, partial colectomies, segmental colectomies.

It has become more and more clear, the absolute need to identify all LS mutation carriers as soon as possible. When posttest genetic counselling risk assessment advice is clinically applied, it can without a doubt save lives. Specific surveillance guided by mutated gene is key treatment-wise, especially when deciding the best surgical plan for young patients. Health care professionals have to recognize and offer the best care of treatment to these individuals and their families, hence they are facing a lifetime of tangible cancer risk.

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