REVIEW

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Major Hereditary Gastrointestinal Cancer Syndromes: a Narrative Review

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ABSTRACT

Gastrointestinal cancer is one of the major causes of death worldwide. Hereditary gastrointestinal cancer syndromes constitute about 5-10% of all cancers. About 20-25% of undiagnosed cases have a possible hereditary component, which is not yet established. In the last few decades, the advance in genomics has led to the discovery of multiple cancer predisposition genes in gastrointestinal cancer. Physicians should be aware of these syndromes to identify high-risk patients and offer genetic testing to prevent cancer death. In this review, we describe clinical manifestations, genetic testing and its challenges, diagnosis and management of the major hereditary gastrointestinal cancer syndromes.

Key words: Hereditary gastrointestinal cancer – Lynch syndrome – FAP – FAMMM – HDGC.

Abbreviations: ACG: American College of Gastroenterology; AFAP: attenuated FAP; APC: adenomatous polyposis coli; CDH1: E-cadherin; CHRPE: congenital hypertrophy of the retinal pigment epithelium; CRC: colorectal cancer; FAMMM: Familial atypical multiple mole melanoma; FAP: Familial adenomatous polyposis; GC: gastric cancer; HDGC: Hereditary diffuse gastric cancer; IHC: immunohistochemical; IPAA: ileal pouch–anal anastomosis; IRA: ileorectal anastomosis; MSI: microsatellite instability; MMR: mismatch repair; miRNA: micro RNA.

INTRODUCTION

Hereditary cancer syndromes are the result of specific inherited genetic mutations that contribute to a person's lifetime risk of cancer. Sometimes, cancer-predisposing mutations are inherited giving rise to hereditary cancer syndromes [1]. Identification of an inherited cancer syndrome has important implications for patients already diagnosed with cancer apart from family [2]. Recent advances in genomics have successfully identified cancer predisposing genes such as DNA mismatch repair genes in Lynch syndrome and the adenomatous polyposis coli (APC) gene in familial adenomatous polyposis (FAP) etc [3]. Hereditary cancer syndromes need a multidisciplinary approach. This includes detailed family history, genetic testing, counseling and screening [4]. Sometimes, a strong family history is not always present in people with hereditary cancer syndromes, which can be due to small family size, incomplete penetrance, or the germline mutations arising spontaneously [1]. This poses the biggest challenge for the physicians to identify the individuals with an increased cancer risk.

Genetic testing is essential to identify cancer predisposition genes in high-risk individuals. Genetic counseling will help the patients understand the significance of genetic testing and its potential to decrease the mortality in a hereditary cancer syndrome [5]. Regular surveillance and appropriate screening have shown to be effective in reducing the mortality in hereditary cancer syndromes. Gastrointestinal cancer syndromes constitute major part of the hereditary cancer syndromes [1]. In this review, we describe genetics, clinical features, and management of major hereditary gastrointestinal cancer syndromes (see Table I).

LYNCH SYNDROME

Lynch syndrome, which was initially termed as Hereditary Nonpolyposis Colorectal Cancer (HNPCC) was first described by Warthin in 1913 [6]. Later in 1991, the International

Table I. Hereditary gastrointestinal cancer syndromes

Syndrome	Mutated gene	Penetrance	Screening	References
Lynch Syndrome	MLH1, MSH2, PMS2, MSH6, EpCAM	CRC 22–74 % GC 0.7–11 %	colorectum, endometrium, ovary, small bowel, stomach, renal pelvis and ureter, biliary tract, brain tumors, breast, sebaceous skin tumors	[7, 33]
Familial Adenomatous Polyposis	APC	CRC 100 % GC 2.2–2.8 %	colorectum, duodenum, papillary thyroid, hepatoblastoma, medulloblastoma	[14, 33]
Familial Atypical Multiple Mole Melanoma	CDKN2A	PC 11.7%	malignant melanoma, pancreas, lung, breast	[21, 34]
Hereditary Diffuse Gastric Cancer	CDH1	CRC 1 % GC 67–83 %	stomach (diffuse type), lobular breast cancer	[29, 33]

CRC: colorectal cancer; GC: gastric cancer.

collaborative group came up with Amsterdam criteria for the diagnosis of HNPCC, which were later broadened to Amsterdam II criteria to include extracolonic tumors. After thorough genomic search and linkage analysis, it was demonstrated that people with Lynch syndrome had ubiquitous somatic mutations in simple repeated sequences, which were later described as microsatellite instability (MSI) [7]. This research has further lead to the discovery of mismatch repair (MMR) genes [7]. Thus, MSI is a hallmark of Lynch syndrome, where defective MMR causes variations in microsatellites thereby causing a change in the genome length [8].

Genetics

Lynch syndrome is caused by germline mutations in DNA mismatch repair (MMR) genes such as MLH1, MSH2, MSH6, or PMS2 [5]. Microsatellites are repeats in DNA sequences distributed throughout the human genome. They are also found in sporadic colorectal cancer (CRC) through methylation of the MLH1 promoter region [8]. Somatic occurrences of MSI can be detected through the concurrent presence of BRAF somatic V600E mutation, which can rule out Lynch syndrome [8].

Around 30% of patients with a clinical diagnosis of Lynch syndrome do not show a germline mutation within a MMR gene [9]. Some of these patients have been shown to carry constitutional epimutation of MLH1 or MSH2, which means that there is transcriptional inactivation of the gene. This is important because a cancer inheritance risk varies depending upon whether it is a germline mutation or epimutation. MSH2 epimutations show tissue-specific mosaicism, which means increased methylation occurs in the epithelial tissue such as colonic mucosa and less methylation occurs in other tissues [9]. These MSH2 epimutations occur through germline deletions in the upstream EPCAM gene, so these are transmitted in an autosomal dominant manner [9].

Constitutional epimutations in MLH1 are two types, which include primary and secondary epimutations. The primary constitutional epimutations are characterized by dense methylation of all somatic tissues and can be reversed between generations. They follow a non-Mendelian inheritance pattern, which means that the phenotype is hard to predict in subsequent generations. On the other hand, secondary constitutional MLH1 epimutations are caused by cis-acting DNA sequence alterations and therefore follow a Mendelian pattern of inheritance where the disease phenotypes are more predictable. However, this type of epimutation shows marked somatic hypermosaicism between tissues and families, which can also further result in varied phenotypes [9].

Clinical presentation

Lynch syndrome accounts for about 2% to 4% of CRCs. It increases the lifetime risk of CRC (70-80%), endometrial (50-60%), stomach (13-19%) and ovarian (9-14%) cancers [10]. Hampel et al. studied 1566 unresected CCR patients, among which 44 (2.8%) patients manifested Lynch syndrome [7].

Other extracolonic cancers to which Lynch syndrome predisposes include carcinoma of the renal pelvis and ureter, small bowel, hepatobiliary tract, and pancreas [7]. Turcot's syndrome, one of the variants of Lynch syndrome is a genetic disease characterized by a broad spectrum of colorectal findings such as adenomas to colorectal cancers [11]. These adenomas tend to occur at an early age and are associated with brain tumors such as glioma, medulloblastoma, and astrocytoma. Another variant known as Muir-Torre syndrome predisposes to colorectal and genitourinary cancers along with sebaceous neoplasm and keratoacanthomas [12].

Screening

Lynch syndrome screening has been increasing since 2000. Universal screening of Lynch syndrome has proven to be cost effective in identifying high-risk families and subsequent prevention of colonic and extracolonic tumors [7]. In people diagnosed with Lynch syndrome, initiating colonoscopy is recommended at age 20-25 years or 2-5 years prior to the earliest case of CRC in the family if it is diagnosed before the age of 25 years, and repeated every 1-2 years [10]. Full colonoscopy is required, as at least 70% of syndrome-related CRCs are proximal to the splenic flexure [7]. Endometrial and ovarian cancer screening may be performed on a yearly basis from age 30-35 years with gynecological examination and pelvic ultrasound [10]. Also, immunohistochemical (IHC) staining provides a cost effective way for assessing the protein expression of the MLH1, MSH2, MSH6, and PMS2 genes [8].

Germline testing can be performed to identify the gene if IHC fails to detect the protein [8].

Management

Identification of the Lynch syndrome has both preventive and therapeutic implications [7]. Women who carry a germline mutation for Lynch syndrome have a 40-60% increased risk of endometrial cancer [7]. Though it is recommended to start screening for endometrial and ovarian cancer at age 30-35 years, there is no literature available to support the survival benefit. Studies have shown a significant reduction in endometrial and ovarian cancers among those patients with Lynch syndrome who underwent prophylactic surgery vs those who did not have surgical prophylaxis [7]. So, prophylactic hysterectomy and oophorectomy can be considered when childbearing is completed to decrease the risk of cancer [7]. Research is being carried out to study the synthetic lethality between MMR and other mutations and their role in the response to PARP inhibitors and methotrexate [13].

FAMILIAL ADENOMATOUS POLYPOSIS

Familial Adenomatous Polyposis (FAP) is a highly penetrant autosomal dominant disorder, caused by an inherited mutation in the tumor suppressor adenomatous polyposis coli (APC) gene on 5q21 [14]. It is characterized by hundreds to thousands of polyps in the colon with the mean age of diagnosis being 16 years [15]. Attenuated FAP (AFAP) is a variant of FAP manifesting fewer polyps and generally a later age of onset [3].

Genetics

The APC gene controls the cell proliferation through transcription genes such as cyclin D1 and c myc [16]. The APC gene also helps to suppress tumorigenesis by inhibiting cell cycle progression from G0/G1 to the S phase [8]. Most of the genetic alterations in the APC gene are truncations or nonsense mutations, which have been utilized for genetic testing such as identification of truncated protein in a process called protein truncated testing (PTT) [16]. Recently, techniques such as multiplex ligation dependent probe amplification (MLPA) have been employed to detect partial or complete loss of the gene, and denaturing high-performance liquid chromatography (dHPLC) is helpful in detecting missense mutations which are usually missed in PTT [16]. Other genetic mutations associated with familial polyposis are in MUTYH, a base excision repair gene, and are transmitted through autosomal recessive inheritance [16].

It was mentioned in the literature that epigenetic alterations can also be responsible for carcinogenesis in FAP through hypermethylation of the APC gene. Epigenetics is defined as the changes caused in the phenotype with no actual change in the genetic code. Hypermethylation of the APC gene causes gene silencing and decreased transcription [14]. Most data have shown that APC methylation can rarely lead to mutation-negative FAP and does not result in complete tumor suppressor gene inactivation [17]. Thus, germline mutation of APC occurs in most of the cases and is a major contributor to the carcinogenesis of FAP. Recent studies have shown that micro RNA (miRNA) can function as tumor suppressor genes, decreased expression of which have an important genetic effect on the colorectal carcinogenesis in FAP [17]. More studies are needed to establish its role in the carcinogenesis of FAP.

There is a wide genotype and phenotype variation in people with APC gene mutations depending upon the area of mutation [18]. For example, mutations located in the central part of the gene between codons 1000 and 1400 are associated with classic FAP, whereas mutations occurring in the peripheral 5‘ and 3‘ regions are associated with AFAP. Mutations between codons 311 and 411 and in the 3‘ region are associated with congenital hypertrophy of the retinal pigment epithelium (CHRPE) whereas mutations after codon 1400 are associated with osteomas and desmoid tumors [16]. Genotype and phenotype variations seen in APC gene mutations can be partially explained by the presence of modifying genes, environmental factors, along with somatic mosaicism which means the presence of genetically different cell populations in the same tissue [5]. According to a retrospective study done by Asertz et al., 6 out of 8 patients who had a mild phenotype despite the presence of severe phenotypic mutations had somatic mosaicism, which was determined by Snap shot analysis [5]. According to them, the true incidence of mosaicism is underestimated and some of the deviations from the expected phenotype can be related to it.

Clinical presentation

The hallmark of FAP is the development of hundreds of adenomatous polyps in the colon and rectum usually in adolescence, with an almost inevitable progression to CRC by the age of 35–40 years, significantly younger than sporadic CRCs [8]. A total of 70–80% of tumors occur on the left side of the colon [8]. FAP patients are at higher risk of developing duodenal polyps, gastric fundic polyps, CHRPE, specific to FAP, desmoid tumors, second leading cause of death in FAP, thyroid cancer with the most common histological type being papillary, hepatoblastoma and pancreatic adenocarcinoma. Turcot syndrome and attenuated FAP (AFAP) are considered variants of FAP [8].

Screening

Screening of patients and family members, with timely treatment of affected individuals, has led to a 55% reduction in the occurrence of CRC at diagnosis of FAP with an improvement in cumulative survival for all FAP patients [8]. The American College of Gastroenterology (ACG) recommends annual sigmoidoscopy, beginning at the age of 10–12 years for patients with a genetic diagnosis of FAP, or at-risk family members who have not undergone genetic testing [8].

Management

Surgical options for polyposis in FAP include a subtotal colectomy with ileorectal anastomosis (IRA), a total proctocolectomy with a continent ileostomy, or a proctocolectomy with ileoanal pouch. Subtotal colectomy with IRA is a simpler technique associated with less perioperative complications [16]. It is well tolerated in most patients although the residual rectal mucosa that is left after the surgery keeps the patient at higher risk of developing CRC, with cumulative risk increasing with age up to 29% by 50 years [16]. Some

people argue that the risk of dying of rectal cancer after IRA is only 2% after a 15-year follow-up, suggesting that IRA should be preferred [11]. People who have undergone IRA should undergo surveillance of the rectum every 6 months [18].

Proctocolectomy with an ileal pouch–anal anastomosis (IPAA) is another alternative approach to IRA, which involves complete resection of colorectal mucosa while preserving anal defecation [16]. Patients are at a lower risk of developing rectal cancer after IPAA, but it is associated with complications such as pouch failure, the marked reduction in female fertility, incontinence and pelvic adhesions [18]. Nieuwenhuis et al. proposed to utilize the mutational analysis in FAP patients to support the surgical decision between IRA and IPAA [19]. They recommended IPAA in patients with mutations between codon 1250-1464 of the APC gene which are observed to have severe FAP phenotype and IRA in patients with intermediate and AFAP phenotype. Though mutation analysis is important to identify people at risk, its utilization in clinical management is still controversial due to phenotypic variations in individuals with similar germline mutations [19]. According to Freidl et al., clinical management should be based on the degree of colonic polyposis (greater than 500 colonic adenomas, greater than 20 rectal adenomas), the presence of rectal cancer, poor access to follow-up, and incidence of desmoid tumors along with mutations involving codons 1251-1309 [18, 19]. Chemoprevention with cyclooxygenase-2 (COX-2) inhibitors has been studied in randomized controlled trials, which showed a 30% tumor burden reduction in patients who took COX-2 inhibitors when compared to the control group [5]. It has also been found that there is no significant benefit with combination therapy when compared to single agent therapy in reducing the tumor burden [5].

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA

This syndrome is included in a discussion of hereditary gastrointestinal syndromes because of its association with pancreatic cancer. The estimated number of cases of melanoma of the skin diagnosed in the United States in 2015 was 73,870, with the estimated number of deaths being 9,940 [20]. Among these, 5-10% cases have a hereditary predisposition [20]. Around 20-40% of people with familial melanoma worldwide have a germline mutation in the CDKN2A gene, whereas germline mutations in another gene, CDK4, are seen in only about 1% of melanoma-prone families [20]. FAMMM should be considered in people with multiple nevi (more than 50), history of cutaneous melanoma in first and second-degree relatives with early onset or a family history of melanoma, pancreatic cancer and astrocytoma [20, 21].

Genetics

CDKN2A is located on chromosome 9, alterations of which are associated with the FAMMM syndrome [21]. CDKN2A is comprised of 4 exons, which encode for two proteins, p16 and p14ARF [20]. p16 inhibits phosphorylation of retinoblastoma (RB) protein through cyclin-dependent kinase 4 (CKD4) and CDK6. Accumulation of hypo phosphorylated RB protein prevents the transcription factor E2F1, which triggers G1 to S transition thereby increasing tumorigenesis [21], whereas p14ARF antagonizes HDM2 thereby increasing the proteasomal degradation of p53 (a tumor suppressor gene) [21]. Mutations in CDKN2A lead to a loss of p14ARF and p16 function which increases tumorigenesis risk [21].

Clinical presentation

The association between FAMMM and pancreatic cancer is well established with 13-22 times higher risk than the average population, especially in people with the CDKN2A mutation [21]. Other cancers associated with CDKN2A mutations are stomach, lung, and colon cancer [21]. Patients who harbor these mutations have a higher risk of melanoma with mutation penetrance varying in different geographic regions, which could be attributed to sun exposure and genetic factors. For example, estimated penetrance rates are 50-76% in the United States compared with penetrance rates of 13-58% in Europe [21]. Studies have not established any definitive role of CDKN2A mutation in the age of onset of cancer.

Screening

An individual who is found to have the mutation needs to undergo regular surveillance and should be referred to a gastroenterologist to discuss the risk of pancreatic cancer and its screening. People identified with the FAMMM syndrome should undergo total body examination and dermoscopic examination every 3 to 6 months. Screening in children should be started when they reach late adolescence [21]. Endoscopic ultrasound is the most sensitive and safe option available for pancreatic cancer screening at this time. Some authors suggest that screening should be started at age 50 years with no specific protocol available as of now [21].

Management

Removal of rapidly progressive high-risk nevi is usually recommended in patients with CDKN2A mutation to decrease the risk of melanoma [21]. It is not recommended to remove observable stable nevi since it has not shown to decrease the risk of melanoma [21]. Families should be educated about sun protective measures such as sunscreen, abstaining from tanning beds etc.

HEREDITARY DIFFUSE GASTRIC CANCER

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant disorder, which was described by Guilford in 1998 as an autosomal dominant disorder due to a mutation in the E-cadherin gene, which was seen in 30-50% of the cases [22]. New data by Hansford et al. showed a lower percentage of 19% with the mutation who met the clinical criteria for the diagnosis [22].

Genetics

The E-cadherin (CDH1) gene has been identified in approximately 40% of families showing a pedigree consistent with HDGC and about 80% penetrance consistent with an autosomal dominant mode of inheritance [23]. Hereditary diffuse gastric cancer can predispose to lobular breast cancer

[24]. The pathogenesis of gastric cancer is the result of the interaction between environmental and genetic factors [24, 25].

Gastric cancer is classified into an intestinal type and a diffuse type. *Helicobacter pylori* is one of the major infectious environmental factors that are associated with chronic gastritis and the development of diffuse gastric cancer. Activation of K-ras and β-catenin oncogenes, mutation of the p53 tumor suppressor gene and MSI have been associated with both histological types. Amplification of C-erb and C-met genes has been found in about 10% of both histological types [24, 25]. Somatic mutation of CDH1 has been associated with diffuse gastric cancer specifically [24, 25].

In addition to these known genetic mutations, epigenetics has been found to have a significant clinical impact on the development of gastric neoplasia. The major epigenetic process that plays a role in the pathogenesis of gastric cancer is DNA methylation [24, 25]. DNA methyltransferases (DNMTs) catalyze the modification of cytosine in the CpG islands resulting in inactivation of the gene and repressing transcription. DNA hypermethylation of tumor suppressor genes causes gene silencing and decreases tumor suppressor gene transcription, which plays a major role in gastric carcinogenesis. Histones are highly alkaline, rich in lysine and arginine amino acids that are positively charged and interact with the negatively charged DNA to package it into nucleosomes. In gastric cancer, histone 3 acetylation and methylation of lysine 9 residues on histone 3 have been associated with the silencing of the tumor suppressor gene and subsequent tumorigenesis [24, 25].

CDH1 hypermethylation and downregulation is seen in diffuse gastric cancer and has been associated with the cancer's ability to invade vascular channels and metastasize, predicting a poor prognosis [24, 25]. Hypermethylation of the Death Associated Protein Kinase (DAPK) gene and the suppressor of cytokine signaling-1 (SOCS-1) gene were found to correlate with lymph node metastasis and the high tumor stage in both types of gastric cancer predicting a poor survival [24, 25]. Lysine methylation of H3K9 is associated with advanced tumors and is present in diffuse gastric cancer. Decreased acetylation of H4 correlates with high-grade tumors, a greater extent of lymph node involvement and metastasis. Detecting such hypermethylation loci can be a very important diagnostic tool to detect gastric cancer at an early stage. Furthermore, using treatment modalities, which can target such changes, augments gastric cancer therapy [24, 25].

Corso et al. [24] reported novel alterations of CDH1 in the familial clustering of lobular breast cancer without evidence of diffuse gastric cancer and with no identified BRCA1/2 mutations. Hansford et al. [22] performed panel-based testing involving 55 candidate genes on 144 probands. Novel truncating mutations in the CTNNA1 (β-catenin) gene was found in two unrelated HDGC families. They suggest that CTNNA1 should be considered in screening families with HDGC. A novel BRCA2 truncating variant was found in 1 proband, and also a truncating mutation in PRSS1, an upper gastrointestinal tract-related gene [22]. Diffuse gastric cancer families with BRCA2 mutations would likely benefit from preventive and therapeutic measures. In studying an HDGC family negative for the CDH1 mutation, these authors identified three candidate genes, the most promising of which is INSR, which may affect E-cadherin glycosylation [23]. Hansford et al. suggested that unexplained cases of HDGC are likely attributable to a combination of mutations in as yet unidentified genes, phenocopies among families, or other abnormalities related to the CDH1 locus or pathway [22].

Clinical presentation

Per the National Cancer Institute, there were an estimated 79,843 people living with stomach cancer in the United States with a lifetime risk of 0.9 percent and 26,370 newly diagnosed cases in 2013 [22]. Most of the gastric cancers are sporadic with only 1-3% seen as inherited cancer syndromes [22]. The intestinal variant of gastric cancer is related to environmental factors such as infections but can be seen in hereditary gastrointestinal syndromes such as Lynch syndrome, FAP, and Peutz-Jeghers syndrome. The diffuse variant is related to host factors and is seen in cases of HDGC [28, 29]. People with the presence of two or more cases of diffuse gastric cancer in their family, with at least one diagnosed at an age younger than 50 years, three or more cases documented in first or second-degree relatives independent of age of onset, diffuse gastric cancer diagnosed at <40 years, or a personal or family history of diffuse gastric cancer and lobular breast cancer with one diagnosed at <50 years, should be evaluated for HDGC per the ACG in their 2015 guidelines [30]. The presence of a CDH1 mutation will yield an 80 percent lifetime risk of gastric cancer for both men and women by the age of 80 years and a 60 percent lifetime risk of lobular breast cancer in women by the age of 80 years [27]. There is no significantly increased risk for any other cancer types, but there is increasing evidence of a higher risk for colon cancer [27, 30].

Screening

For now, genetic testing for CDH1 mutations must be offered for families who meet the HDGC criteria. Screening is usually done at the age of 18 years which is the age of consent, but in HDGC, 16 years is an acceptable age for testing because of reported cases of gastric cancer in patients in their mid-teens in New Zealand [27].

Management

The management of a CDH1 mutation carrier is to offer a prophylactic gastrectomy after the age of 20 years because of the high penetrance rate of the gene, the lifetime risk of developing gastric cancer, and the difficulty of diagnosing early diffuse gastric cancer. In cases where an individual declines a prophylactic gastrectomy, an annual surveillance endoscopy beginning 5–10 years before the earliest cancer diagnosis in the family should be offered in a specialized center with endoscopists and pathologists experienced with such cases, but there are no sufficient data supporting this approach yet [28, 30]. Endoscopy as a screening tool should be offered for individuals who meet the HDGC criteria but whose genetic testing comes back negative for the CDH1 mutation or who carry a mutation of undetermined significance [28, 30]. Given the high risk of lobular breast cancer, ACG recommends breast cancer surveillance in women beginning at age 35 years with annual mammography, breast MRI and clinical breast

examination every 6 months [28, 30]. Given the emerging data of colon cancer in such a population, ACG recommends colonoscopy starting at the age of 40 years.

CONCLUSION

The number of hereditary cancer syndromes will considerably increase in the near future given the recent advances in genomics. With increasing understanding of targeted therapy against specific gene mutations, germline mutations will be increasingly used in the future for optimal therapy [31]. Though hereditary gastrointestinal cancer syndromes constitute a lower percentage of total cancer diagnoses, more emphasis is warranted to increase awareness among the population to decrease the cancer related mortality. Genetic testing can also be considered in individuals with metastatic gastrointestinal cancer, which will open the door for unidentified familial syndromes [32].

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