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HNPCC (LYNCH SYNDROME): DIFFERENTIAL DIAGNOSIS, MOLECULAR GENETICS, SURVEILLANCE, AND MANAGEMENT

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Approximately 5-10% of the total colorectal cancer (CRC) burden is due to primary Mendelian inheritance factors. This estimate poses a major public health problem when considering that the annual incidence of CRC in the United States is approximately 147,500 (72,800 males; 74,700 females) with approximately 57,100 deaths (28,300 males; 28,800 females).1 These estimates would yield 7,375 to 14,750 cases annually of primarily Mendelian inherited CRC, and 2,855 to 5,710 deaths from same. These estimates may be conservative when considering the existence of low-penetrant genes such as the Ashkenazi I1307K mutation2 and the recently described recessive form of FAP-like families due to the MYH mutation.3,4

The estimated annual worldwide CRC incidence is 944,717 with a mortality of 492,411. Colorectal cancer's annual incidence in Brazil is estimated at 18,554, with a mortality of 9,065. The estimate of 5-10% of all CRCs being due primarily to hereditary factors would also apply to these figures.

Understanding the role of genetics in the etiology of CRC has increased rapidly during the past decade. This knowledge explosion has, in a major way, been due to the prodigious advances in molecular genetics. Indeed, this information has evolved so rapidly that it has outpaced the ability of physicians to keep abreast of these fast-breaking events.

"Familial" CRC (two or more first-degree relatives with CRC) and "sporadic" CRC (a single case of CRC in a set of first-degree relatives) are relatively crude terms since they do not take into consideration the presence of cancer of other organ sites, low-penetrant mutations, possible autosomal recessive inheritance, the general lack of genetic informativeness which may occur in a small family, adoption, false paternity, outright denial, and/or the lack of cooperation of family members and their physicians. Collectively, these factors may obfuscate, and thereby underestimate, the true incidence rate of the genetic susceptibility to CRC.

Heterogeneity of Hereditary CRC

Hereditary CRC can be divided into two groups based upon molecular features. Specifically, tumors, "...that exhibit microsatellite instability (MIN) tend to occur in the right colon, have diploid DNA, carry characteristic mutations (transforming growth factor b Type II receptor, BAX) and behave indolently. Hereditary non-polyposis colorectal cancer (HNPCC) epitomises this route of tumour development. Conversely, tumours with chromosomal instability (CIN) tend to be left-sided, have aneuploid DNA, carry characteristic mutations (K-ras, APC, p53) and behave aggressively. Familial adenomatous polyposis (FAP) epitomises this type of tumour."5

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Lynch Syndrome

Lynch syndrome (HNPCC) is the most commonly occurring hereditary syndrome that predisposes to CRC.6 It accounts for somewhere between 2-7% (2,940 and 10,290) of the CRC cases in the U.S. annually.6 Its diagnosis is frequently difficult because, with the exception of cutaneous stigmata in its Muir-Torre syndrome (MTS) variant,7,8 it lacks phenotypic signs that might facilitate its presymptomatic diagnosis.

While the literature has increased enormously dealing with diagnostic guidelines for HNPCC,9-11 its surveillance, management,6,12,13 molecular genetic testing,14,15 as well as the ethical and malpractice issues that impact on these concerns,16 the description of barriers to its diagnosis, management, and compliance of at-risk patients to these recommendations have been lacking.

The original definitions by clinical and pedigree criteria such as the more stringent Amsterdam criteria9 or the less stringent Amsterdam II criteria10 are valid today. However, in many situations the occurrence of HNPCC-associated cancers, especially in small families, cancer of markedly early onset, or multiple cancers in one individual, should alert the clinician to the possibility of HNPCC.

The algorithm (Figure 1) provides a partial explanation of the steps that are taken in the workup of a potential Lynch syndrome patient, inclusive of family history, molecular genetic testing, and how one proceeds with genetic counseling, surveillance, and management.

Cancer Genetics and Reduction in Morbidity and Mortality

How can we help reduce cancer morbidity and mortality among high-risk patients? The solution in some instances can be relatively simple through identification of individuals who, by virtue of their position in their family pedigrees, show a remarkably increased risk. The identification process begins by systematically recording the family history with emphasis on cancer of all anatomic sites. Ideally, this history should be corroborated with medical and pathology documents whenever possible. Central to this is a knowledgeable physician who can interpret the pedigree, make a hereditary cancer syndrome diagnosis should it be present, and then proceed with highly targeted surveillance and management strategies. Although this is the ideal situation, we nevertheless must deal with the fact that the cancer family history, although potentially the most cost-beneficial component of a patient's medical work-up, is often neglected in the average clinical practice setting.17,18 Ideally, a presumptive hereditary cancer syndrome diagnosis can be confirmed by molecular genetic testing of an affected individual in some of those disorders where germ-line mutations have been identified.

Clinical Features

Salient features of HNPCC, the most common form of hereditary CRC, include multiple generations affected with CRC at an early age (mean ^{a} 44 years) with right-sided CRC predominance (^{a} 70% proximal to the splenic flexure), and a significant excess of synchronous (multiple CRC at, or within six months of, surgical resection for CRC) and metachronous (CRC occurring more than six months from time of surgery) CRCs.12 In addition, there is an excess of extracolonic cancers, namely, carcinoma of the endometrium (second only to CRC in frequency), ovary, stomach (particularly in Asian countries such as Japan and Korea19), small bowel, pancreas, hepatobiliary tract, brain, and upper uro-epithelial tract.20,21 There is also an apparent statistical deficit of lung cancer, with correction for cigarette smoking,20 which, while not proven, merits further research. HNPCC patients may also manifest sebaceous adenomas, sebaceous carcinomas, and/or multiple keratoacanthomas, findings consonant with the Muir-Torre syndrome variant.8,12

CRC Pathology

When compared to sporadic CRC, CRC tumors in HNPCC are more often poorly differentiated, with an excess of mucoid and signet-cell features, a Crohn's-like reaction, and the presence of infiltrating lymphocytes within the tumor.22-25

Accelerated carcinogenesis occurs in HNPCC, wherein a tiny colonic adenoma may emerge into a carcinoma within two to three years, as opposed to this same process taking eight to ten years in the general population.12,25 Hence, our recommendation for annual colonoscopy as discussed below.

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Molecular Genetics and Lynch Syndrome

MMR gene mutation analysis has provided estimates of the proportion of families with a family history consonant with HNPCC, that carry an MMR mutation. These estimates vary between 40-80% for Amsterdam I families and 5-50% for Amsterdam II families.26,27 Among Amsterdam I and II families, as well as in other families having pedigrees consistent with HNPCC but not meeting formal criteria, families will be found that do not harbor a known MMR mutation. This is consistent with the notions that in such families other genes, not yet discovered, may be responsible and/or that the aggregation of cancers may be caused by environmental factors or be due to chance.14

A Clinical-Molecular Genetic Model

HNPCC is caused by a germline mutation in an MMR gene. Two genes, MLH1 and MSH2, account for almost 90% of all identified mutations. MSH6 accounts for almost 10%, but its share of typical versus less typical HNPCC remains to be determined.28,29 For diagnostic purposes it is usually sufficient to consider primarily just MLH1 and MSH2, and test other genes only if mutations are not found in these two.

More research is needed to aid in the elucidation of hereditary CRC and the ultimate translation of this knowledge into clinical practice, with the primary goal of early diagnosis and prevention. Identification of the culprit predisposing germ-line mutation will determine who is versus who is not a candidate for participation in highly targeted cancer surveillance and management programs.

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