

Hereditary Non-Polyposis Colorectal Cancer (Syndrome HNPCC)

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Abstract

Hereditary non-polyposis colorectal cancer (HNPCC) is a trait subjected to autosomal dominant transmission. Its diagnosis is based on the presence of three criteria, defined in 1991 in Amsterdam, and revised in 1999: 1) at least 3 subjects afflicted with histologically proven cancers belonging to the narrow spectrum of the HNPCC syndrome (hereditary predisposition to colorectal and endometrial adenocarcinomas) 2) paired with a first-degree family relationship over at least 2 generations; 3) at least one of the cancers diagnosed before the age of 50 years.

In the families identified based on these criteria, the affected subjects primarily develop colorectal, with or without endometrial cancers, with a cumulative risk of 70–80% at 70 years. Monitoring by colonoscopy is recommended every 2 years, as of 20 years of age, for individuals carrying a constitutional mutation in the MSH2 (MutS homolog 2, 16 exons), MLH1 (MutL homolog 1, 19 exons) or MSH6 (2p16, 10 exons) gene. Gynecological monitoring of women over 30 years old is also recommended. The treatment of these cancers is the same as that given in the absence of any predisposition. No preventive treatment exists. The gene(s), whose mutation(s) is/are associated with the existence of an HNPCC syndrome belong to the family of DNA mismatch repair (MMR) genes, that is to say in the control of replication accuracy: MSH2, MLH1 and MSH6 are implicated, in order of decreasing frequency, in respectively, 35, 25 and 2% of the cases. No genetic mutation has been found in about a third of the patients.

Key words

Hereditary predisposition – cancer – colon – endometrium – mismatch repair (MMR) genes – microsatellite instability (MSI) genotype – constitutional mutation – predictive genetic test – screening

Hereditary colorectal cancer without polyposis.

Name of the disease and synonyms

Non-polyposis colon cancer

Hereditary non-polyposis colorectal cancer (HNPCC) syndrome

Clinical definition

The HNPCC syndrome is a predisposition for hereditary cancer, clinically defined by the

Amsterdam criteria established in 1991, modified as the 1999 Amsterdam II criteria, which combine individual and genealogical information: 1) at least 3 subjects with histologically proven cancers corresponding to the narrow spectrum of the HNPCC syndrome (colon, rectum and/or endometrium, small intestine and/or urinary tract); 2) paired with a first-degree family relationship over at least 2 generations; 3) at least one of the cancers diagnosed before the age of 50 years. The tumors developing within the setting of a familial predisposition for HNPCC are most frequently the consequence of a constitutional mutation of DNA mismatch repair (*MMR*) gene, associated with tumor-cell phenotype called MSI, for microsatellite instability. To improve the sensitivity of detection of patients carrying a deleterious mutation in an *MMR* gene among cancer patients, other parameters predictive of the presence of this genomic instability have since been advanced (Bethesda conference). Patients with an HNPCC syndrome also run a moderate risk of developing cancers of the ovary, [stomach](#) and bile duct epithelium, which defines the broad tumor spectrum. [Cutaneous](#) and [cerebral](#) tumors have also been described in HNPCC syndrome families, which have been given the names of [Muir-Torre](#) and [Turcot syndromes](#), respectively, even though they do not carry distinct genetic predispositions.

Evolution

The risk of developing a cancer at 70 years of age for patients carrying a deleterious constitutional mutation of an *MMR* gene, regardless of which one, can be estimated as follows:

colon and rectum: 50–60% (men: 70–80%; women: 30–40%)

endometrium: approximately 10%

Ovaries: approximately 8%

Urothelium: approximately 5%

Bile ducts: approximately 5%.

Although the relative risk of cancer of the small intestine is very high, the absolute risk remains low, in light of the rarity of this localization in the general population. No single gene has been shown to have a strong impact on the level of these risks. Consultation with an oncogeneticist is strongly recommended for every patient developing a cancer falling within this broad spectrum before 40 years of age, before 60 years if the cancer has an MSI phenotype, or in the case of a prior cancer or a broad-spectrum cancer in a first-degree relative.

Type of hereditary transmission

The HNPCC syndrome carries a hereditary predisposition for cancer that is inherited by autosomal dominant transmission. According to

the initial Amsterdam criteria, the frequency of the HNPCC syndrome is estimated to be between 1 and 2% of the colorectal cancer patients under 60 years old. However, the recognized lack of sensitivity and reliability of the Amsterdam criteria require that the factors for identifying predisposed individuals need to be extended (see above).

Biochemical basis

The tumors developing within the framework of an HNPCC syndrome have an unstable phenotype, always seen in colorectal cancers associated with inactivation of the main *MMR* genes (*MSH2*, *MLH1*, *MSH6*). The aim of this phenotypic characterization of the tumor cells is to identify, among patients with cancers included in this broad spectrum, the subgroup that could benefit from a search for a constitutional deleterious mutation in their *MMR* gene(s). Phenotyping with molecular genetics techniques was standardized at an international conference organized by the National Institutes of Health (NIH) and the most recent recommendations were published in the *Journal of the National Cancer Institute* in 2004.

Genes

Localization and identification of the responsible gene(s)

Early genetic linkage studies demonstrated the genetic heterogeneity of this syndrome by identifying 2 responsible loci: chromosome 2p15–16 (subsequently redefined as chromosome 2p22–21) and chromosome 3p21. The genes corresponding to these loci, respectively called *MSH2* (*MutS homolog 2*, 16 exons) and *MLH1* (*MutL homolog 1*, 19 exons), could rapidly be identified because of their respective homologies with bacterial genes *MutS* and *MutL*, involved in DNA mismatch repair. In HNPCC syndrome families, constitutional deleterious mutations have since been identified in *MSH6* (chromosome 2p16, 10 exons), another homologue of *MutS*.

Mutations

Linkage studies and then studies on the deleterious mutations showed that more than half of HNPCC cases could be attributed to constitutional mutations in *MSH2* and/or *MLH1*. Approximately 20% of the families with typical HNPCC syndrome, without detectable mutations in *MSH2* and/or *MLH1*, have a genomic rearrangement of the *MSH2* gene. The *MSH6* gene is implicated in approximately 4–5% of the families.

Diagnostic methods

Clinical

The clinical diagnosis of HNPCC syndrome relies on the number of individual and familial factors present, as defined in the Amsterdam criteria.

Biochemical

No biochemical test is able to make the diagnosis.

Genetics

To predict the presence of the disease, the molecular diagnosis of HNPCC syndrome requires the entire decoding *MSH2* and *MLH1* genes. Should this first analysis be negative, less frequent mutations should be sought in families satisfying the indications for such an investigation, i.e., *MSH2* genomic rearrangement and punctual mutations in the *MSH6* gene. A more thorough examination of these 3 genes (analyses of the promoters, their expression, their genomic structure) can only be warranted in the presence of very strong histological and clinical arguments; it will be guided by the results of somatic, molecular and immunohistochemical analyses that should be conducted in a specialized laboratory.

Genetic counseling

It is currently considered legitimate to offer analysis to individuals for whom the *a priori* probability of finding a deleterious mutation exceeds 0.20 (risk of colorectal cancer equal to at least 4 times that of the general population), and unacceptable when this risk is below 0.10 (the risk of colorectal cancer is at most twice that of the general population). Genetic testing should be offered to individuals with a broad-spectrum cancer meeting the following criteria:

- the extended Amsterdam II criteria;
- diagnosis before 40 years of age;
- MSI cancer with 'extinction' of *MSH2* and/or *MSH6* protein(s);
- MSI cancer of the descending colon or rectum;
- Diagnosis before 60 years of age with a personal history or a first-degree relative with a broad-spectrum cancer.

The management possibilities reflect our current understanding of the disease. Except for particular situations, they are proposed to individuals whose personal genetic risk was analyzed by molecular biology or whose probability of having a hereditary predisposition for an HNPCC broad-spectrum cancer is high (above 0.20). It is important to recall that, in individuals carrying constitutional deleterious mutation(s) in their main *MMR* gene(s), the absence of a known significant genotype-phenotype correlation justifies not taking into consideration age at the time of appearance or localization of the cancers in a family in the management propositions. On the other hand,

this approach should be nuanced for families in which no deleterious mutation has been identified, especially when the tumors are not MSI cancers.

Prenatal diagnosis

Carrying out these analyses in minors should be limited to those pathologies susceptible of being managed before 18 years of age, which is not the case for the HNPCC syndrome.

Therapeutic perspectives

Screening for colorectal tumors is important for individuals carrying a deleterious mutation in one of the main *MMR* genes, for example in first-degree relatives of colorectal cancer patients, whose familial history corresponds to the clinical definition of HNPCC syndrome according to Amsterdam II; this screening should consist of colonoscopy, starting at the latest at 25 years of age, but probably not before 20 years, and should be repeated every 2 years. After each colonoscopy, it is recommended that the examination be completed by using a dye, like indigo carmine. In contrast, no prophylactic surgical intervention is recommended. Women carriers of a mutation in their *MSH2*, *MLH1* or *MSH6* gene should undergo an annual gynecological examination as of 30 years of age, completed by pelvic ultrasonography. Should the findings be abnormal, additional examinations, hysteroscopy or hysterosonography, should be undertaken to establish the diagnosis.

The treatment of these cancers is the same as that proposed in the absence of any known genetic predisposition. In terms of chemoprevention, one study conducted on the general population compared 2 groups, 1 taking aspirin daily and other not. The results of that study showed a beneficial effect of daily aspirin ingestion. Aspirin is currently being investigated in individuals with a high risk of colorectal cancer (the CAPP2 study *i.e.* Colorectal Adenoma/carcinoma Prevention Program), as in the HNPCC syndrome, but the results are not yet available.

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