Review article

Lynch syndrome: genetics and surgery

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ABSTRACT

Hereditary nonpolyposis colorectal cancer or Lynch Syndrome, caused by germinal mutations in mismatch deoxyribonucleic acid (DNA) repair genes, is the most common form of hereditary colorectal cancer. The identification of these individuals is not easy and is based on clinical and molecular criteria. A review is presented on the genetics and diagnosis in Lynch Syndrome, as well as on its surgical management and prevention.

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Colorectal cancer
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Surgery

Introduction

Eighty per cent of colorectal cancers are sporadic, 10% are familial and the remaining 5%-10% are hereditary. The most common hereditary colorectal cancers are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC)2 (Figure 1). The name Lynch Syndrome is preferred for families that have mutation in one of the DNA mismatch repair (MMR) genes. The main characteristics of Lynch Syndrome are that colorectal cancer...
develops at an early age (around 45 years old), is likely to be right-sided for more than 70% of cases, increases the incidence of synchronous and metachronous tumours, presents high carcinogen levels, and an increased risk of extracolonic neoplasia (endometrium, ovary, gastric system, urinary tract, small intestine, brain, hepatobiliary system).3

It is an autosomal dominant disorder, caused by MMR genes, mainly MSH2 and MLH1 (90% of all genes) and less often by MSH6 and PMS2.2

One of the main challenges in clinical practice is to identify MMR carriers so that colorectal cancer can be prevented through genetic counseling.4

Methods

This article has been prepared based on a literature review of relevant Lynch Syndrome-related articles. All articles were found using a bibliographic search on the MEDLINE database, using the following key words: ‘Lynch Syndrome’, ‘Nonpolyposis Colorectal Cancer’, ‘Mismatch Repair Gene’, ‘Diagnosis’, ‘Management’ and ‘Screening’. Articles from September 1992 until March 2010 were included.

Genetics and diagnosis

Conceptually, three possible strategies can be used to identify Lynch Syndrome patients: 1) using clinical criteria; 2) using molecular techniques: microsatellite instability (MSI) and immunohistochemistry (IHC) testing; or 3) a combination of both.

Different criteria have been developed to identify Lynch Syndrome families. The Amsterdam I criteria,5 (Table 1) published in 1991, were pivotal in establishing a definition of Lynch Syndrome, allowing its genetic base to be identified. These criteria only considered the risk of colorectal cancer. However, the Amsterdam II criteria,6 published in 1999, included related extracolonic tumours. Given the low sensitivity of the Amsterdam criteria, and having found Lynch Syndrome’s genetic base, the recently revised Bethesda criteria were designed7 with the aim of identifying colorectal cancer patients. A molecular study of the tumour is performed on these patients to identify DNA-repair deficiencies (MSI testing) or loss of protein expression in the relevant mutation gene (IHC testing) suggesting that a germinal mutation is present. The criteria include family history, age at diagnosis, and the pathologic characteristics that are suggestive of tumour microsatellite instability (Table 1).

As well as the criteria mentioned above, several predictive models have recently been developed to determine the MMR gene mutation carrier status (Barneston,8 PREMM,9 and MMRpro10 models).

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**Table 1 – Revised Amsterdam and Bethesda Criteria**

<table>
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<tr>
<th>Criteria</th>
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<tr>
<td><strong>Amsterdam I Criteria</strong></td>
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<tr>
<td>There are at least three relatives with colorectal cancer, and should meet the following criteria:</td>
</tr>
<tr>
<td>One affected person is a first-degree relative of the other two.</td>
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<tr>
<td>At least two successive generations are affected.</td>
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<tr>
<td>At least one person was diagnosed with colorectal cancer before the age of 50 years.</td>
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<tr>
<td>Familial adenomatous polyposis has been excluded.</td>
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<table>
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<tr>
<th>Revised Bethesda guidelines for MSI testing</th>
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<tbody>
<tr>
<td>Tumours from any of the following should be tested for MSI:</td>
</tr>
<tr>
<td>Individuals with colorectal cancer diagnosed at age &lt;50 years.</td>
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<tr>
<td>Individuals with colorectal cancer with MSI-H, histologically diagnosed at age &lt;50 years of age.</td>
</tr>
<tr>
<td>Colorectal cancer diagnosed in one or various first-degree relatives with HNCP or related tumours at age &lt;50 years.</td>
</tr>
<tr>
<td>Colorectal cancer in one or more first- or second-degree relatives, regardless of age.</td>
</tr>
</tbody>
</table>

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**Figure 1 – Syndromes in which colorectal cancer can appear.**

- FAP, AFAP
- Peutz-Jeghers
- Juvenile polyposis
- Lynch Syndrome
- Familial
- Sporadic
DNA damages continuously and spontaneously occur in all of the body’s cells, during replication in cell division, and as a reaction to agents in the environment. The main alteration in Lynch Syndrome development is the presence of mutations that affect the germline of a given group of genes that is very important for maintaining genome stability (MSH2, MLH1, MSH6 and PMS2 are among the most important). These genes code for proteins involved in recognising mutations in base pairing and mismatch repair to prevent mutations developing. Mutations in this system generate microsatellite instability, representing an authentic genomic instability marker that is found in 90% of HNPPC cases and 15% of sporadic cases.3 Microsatellites are very short DNA segments (usually between 1 and 5 nucleotides long) which repeat in a row along the genome. Loss of genomic stability seems to be a key process which occurs in the first stages of carcinogenesis. DNA is extracted from the patient’s colorectal tumour and healthy tissue to study microsatellite instability. MSI refers to the microsatellite repeat patterns observed when comparing the tumours’ amplified DNA with the normal adjacent tissue. Establishing the MSI condition can sometimes be very imprecise. This is mainly because there is not a single criterion with regards the number of loci that must be analysed to diagnose MSI and the proportion of unstable markers that must be considered for MSI classification. In 1997, 5 MSI markers were proposed for this purpose (BAT-25, BAT-26, D2S123, DSS346, D17S250).11 In compliance with the international criteria, MSI is considered to be high frequency (MSI-H) if 2 or more recommended markers in a row present mutations. MSI is considered low frequency (MSI-L) when a single marker is unstable, and MSI stable (MSI-S) when none of the markers exhibit changes in the sequence length. Some authors11 believe that there are no pathologic or clinical differences between colorectal tumours with MSI-L and MSI-S. MSI-H tumours represent 15% of colorectal cancers and are predominantly located in the proximal colon, have unique histopathological characteristics and are associated with a less aggressive clinical development.12,13

MSI analysis methods vary greatly. Single-strand conformation polymorphism (SSCP) is one of the most used as it is simple and versatile. It is based on the relationship between the electrophoretic mobility of a single-stranded DNA segment and its folded conformation, which in turn depends closely on the nucleotide sequence or the segment size.

Some institutions have introduced MSI testing as a form of initial colorectal cancer screening for diagnosed patients under 50 years, or patients with histological characteristics suggestive of MMR gene mutations. Patients with MSI-H are referred for a molecular genetic study.14

Occasionally families fulfill the Amsterdam I criteria, but do not show any evidence of MSI or repair gene mutation, i.e. tumours are microsatellite-stable. Lindor et al name these families “familial colorectal cancer type X”.15

IHC is another technique employed to diagnose HNPPC. It can either accompany MSI testing or replace it.16 Loss of MMR proteins can be observed in Lynch Syndrome tumours (MLH1 50%, MSH2 39%, MSH6 7%, and PMS2 <4%). Loss of MLH1 expression can generally be associated with the secondary loss of PMS2 expression. Similarly, loss of MSH2 can often be associated with the loss of MSH6. However, isolated loss of MSH6 or PMS2 expression, which indicate these gene mutations, are rare and isolated.13,17 Internal positive controls (stroma, lymphocytes) are used in IHC testing to determine that the absence of expression in a tumour is not due to a technical problem. Loss of expression is considered when IHC staining is not observed in any of the neoplastic cells. Results should determine the presence or absence of expression of each of the proteins. They must be considered unassessable if no suitable internal controls are obtained. Most patients with germinal mutations display the results shown in Table 2 for IHC testing, although false positives and false negatives may also appear. As an initial method, IHC has the advantage of being a simple and cost-effective technique. It is also able to identify the unexpressed protein, and as such the mutated gene. Several studies have shown that when using this technique for MLH1, MSH2, PMS2 and MSH6, Lynch Syndrome diagnosis sensitivity is similar to that of MSI, with values over 90%.16,18

Microsatellite instability and loss of MLH1 expression also occurs in 10%-15% of sporadic colorectal cancers as a result of promoter hypermethylation of this gene. In order to exclude this possibility before carrying out germline MLH1 mutational analysis, it is useful to analyse whether the BRAF V600E mutation is present in the tumour, given that this mutation is associated with MLH1 promoter hypermethylation. The BRAF mutation test can therefore be added to the genetic testing algorithm for Lynch Syndrome before conducting the genetic study.19

Once identified by means of clinical criteria, and using different molecular studies (MSI, IHC, BRAF), the genetic analysis can continue to confirm Lynch Syndrome diagnosis. Peripheral blood lymphocytes DNA is examined for the germline analysis (Figure 2).3,20

The European Expert Group recommends the following to improve hereditary colorectal cancer diagnosis: public information campaigns; complete family study recommended for previously diagnosed patients, with the number of family members affected, type of neoplasia and age at diagnosis; reference guides with specialised genetics centres, and guides with information about familial colorectal cancer and follow-up recommendations; consider MSI or IHC testing in colorectal cancer patients regardless of age at diagnosis with appropriate counselling.21

### Table 2 – Results from immunohistochemistry test, based of germinal mutation

<table>
<thead>
<tr>
<th>Germinal mutation in:</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
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<tbody>
<tr>
<td>MLH1</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>MSH2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
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<tr>
<td>MSH6</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
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<tr>
<td>PMS2</td>
<td>−</td>
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Once Lynch Syndrome has been diagnosed, it should be treated and screened considering the natural history of the syndrome. Colon cancer screening plays an important role, and several studies show how colonoscopy surveillance can benefit these patients.

In a study on HNCPP families, Järvinen et al show that the incidence of invasive colorectal cancer decreased by 63% for asymptomatic patients who underwent colonoscopy surveillance compared with those families that were not screened. Furthermore, mortality decreased for patients who underwent screening and colonoscopy, compared to those who did not. Based on evidence, Lindor et al recommend closely monitoring Lynch Syndrome patients with colonoscopy every 1-2 years, starting at 20-25 years old (or at 30 years for MSH6 families).

Many families fulfill the Amsterdam criteria but have negative MSI and IHC test results. Less regular screening is recommended for these patients, a colonoscopy every 3-5 years, starting at 45 years, or every 5-10 years before the age of the youngest family member diagnosed with colorectal cancer.

The second most frequent cancer after colorectal cancer observed in Lynch Syndrome patients is endometrial carcinoma (40%-60% for women with mutation), then ovarian cancer (12%-15% of women with mutation). Lindor et al recommend transvaginal ultrasound and an annual smear test, starting at 30-35 years.

Studies on screening for extracolonic cancers are limited. European and North-American expert groups recommend:

Screening

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Surgical treatment, surveillance

Patients who have been diagnosed with Lynch Syndrome and have developed colorectal cancer should firstly undergo a complete colonoscopy, as they present a high risk of developing a synchronous tumour. Risk of metachronous cancer should be considered when choosing which surgical technique should be adopted, which is 16% at 10 years in some studies. Extension of the resection has also been much debated during recent years. Although no controlled studies have been conducted, most experts champion subtotal colectomy with ileo-rectal anastomosis. De Von tot Nederveen Cappel et al compare segmental colectomy resection with subtotal colectomy in colorectal cancer patients diagnosed with Lynch Syndrome. The study identified an increase in life expectancy of 2.3 years in young patients (<47 years) who underwent subtotal colectomy. There are limitations in this study because the data are not adjusted to quality of life, but the authors suggest that subtotal resection could improve patients’ quality of life by reducing the need for periodic colonoscopies, and by reducing concerns of a second neoplasm developing. A recent study that compares extended colectomy with limited resections performed on Lynch Syndrome patients does not show any...
Prophylaxis

Secondly, the doctor must decide what therapeutic option should be used for Lynch Syndrome patients who have not developed colorectal cancer. Prophylactic surgery avoids close endoscopic surveillance. The types of prophylactic surgery available would be subtotal colectomy with ileo-rectal anastomosis and proctocolectomy. Post-surgical surveillance is required for subtotal colectomy by means of rectoscopy as the patient might develop metachronous rectal cancer. While most colorectal cancers for Lynch Syndrome patients develop on the right side of the colon, risk of rectal cancer is estimated to be from 11%.32 No studies have recommended practice of prophylactic surgery. However, authors who argue for this type of surgery are supported by the fact that there is an 80% risk of HNCPP patients developing colorectal cancer sometime during their lifetime. Using experienced genetic counsellors during the Lynch Syndrome family counselling session, allows the specialist to use his or her time more efficiently, being able to focus on the clinical treatment.13 That is why, patient(s) and/or families with clinically suspected Lynch Syndrome should be referred to a hereditary cancer unit or genetic counselling to assess their situation.36

During 10-year surveillance, none of the patients who had undergone prophylactic surgery developed ovarian or endometrial cancer, while in the other group 33% developed endometrial cancer and 5.5% ovarian cancer. These data suggest that prophylactic hysterectomy and oophorectomy can be a reasonable option for Lynch Syndrome patients who have already had children, discussing the risks, benefits and limitations related to the procedure.24

Different studies have shown how non-steroidal anti-inflammatories and aspirin effectively reduce the incidence of sporadic adenomatous colorectal polyps and cancer. However, their efficiency for Lynch Syndrome patients is still unknown.24 Oral contraceptives have shown to reduce the risk of ovarian and endometrial cancer in the general public, but there is no data to suggest the benefit in extracolonic cancers in Lynch Syndrome patients. The effect that chemotherapy has on MSI-H and HNCPP patients has been reported in very few studies, yet many show that these patients do not benefit from 5-FU treatment. To date, there is not enough evidence regarding chemotherapy use, meaning that controlled and prospective studies should be conducted for future recommendations.3,24

Genetic counselling

Genetic counselling is a process that provides the patient and his or her family members with information about the risk of developing or transmitting a given genetic susceptibility to developing a neoplasm. The patient or family is also informed about molecular diagnosis testing to prevent it or diagnose it early.35

We should consider the patient's and the family's emotional state, as they generally require psychological support. A detailed and focused session needs at least 60-90 minutes. Using experienced genetic counsellors during the Lynch Syndrome family counselling session, allows the specialist to use his or her time more efficiently, being able to focus on the clinical treatment.13 That is why, patient(s) and/or families with clinically suspected Lynch Syndrome should be referred to a hereditary cancer unit or genetic counselling to assess their situation.36

The genetic counselling process assesses the personal and family risk to hereditary susceptibility to cancer by completing an extensive medical history regarding personal and family events. Risk assessment quality will depend on this family history.

Conflict of interest

The authors affirm that they have no conflict of interest.
REFERENCES


