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• COLORECTAL CANCER •

Clinical characteristics and diagnosis of patients with hereditary nonpolyposis colorectal cancer

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Abstract

AIM: To study the clinical characteristics of hereditary nonpolyposis colorectal cancer (HNPCC) in the Chinese population and discuss the identification and management of the patients with HNPCC.

METHODS: A series of 140 patients with colorectal cancers (CRC) and HNPCC associated tumors from 30 families fulfilling the Amsterdam criteria were analyzed.

RESULTS: A total of 118 patients had CRC. Average age at diagnosis of the first CRC was 45.7 years, 56.8 % and 23.4 % of the first CRC were located proximal to the splenic flexure and in the rectum respectively. Twenty-three (19.5 %) had synchronous and metachronous CRC. Twenty-seven patients were found to have extracolonic tumors. Gastric carcinoma was the most common tumor type in our series (44.4 %).

CONCLUSION: The frequency of HNPCC was 2.6 % in our series of patients. The main features are an excess of early onset with a propensity to involve the proximal colon, and high frequency of multiple foci. Management and surveillance for these patients should be different from sporadic CRC. Contrary to American and European reports, gastric cancer seems more frequent than endometrial cancer in Chinese. It is necessary to formulate a new HNPCC criterion for Chinese patients.

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INTRODUCTION

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is a distinct autosomal dominant syndrome. It accounts for 1-10 % of the total colorectal cancer population[1-9]. On the basis of the absence or presence of extracolonic malignancies, it can be subdivided into Lynch syndrome I (hereditary site specific colorectal cancer) and Lynch syndrome II (colorectal cancer in association with extracolonic cancer)[10,11].

The criteria for clinical diagnosis of HNPCC were established by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) in 1991. These criteria known as the "Amsterdam criteria" are as follows: (1) Histologically verified colorectal cancer in three or more relatives, one of whom is a first-degree relative of the other two; (2) Colorectal cancer involving at least two generations; (3) One or more colorectal cancers diagnosed below age of 50 years. In the present study, 30 Chinese HNPCC families fulfilling the Amsterdam criteria were studied.

MATERIALS AND METHODS

Materials

From September 1994 to December 2001, 30 Chinese HNPCC families that fulfilled the Amsterdam Criteria were registered at the Department of Abdominal Surgery in the Shanghai Cancer Hospital / Institute. Of the 30 identified patients, 8 were found to have colorectal cancer before October 1998 and 5 were diagnosed and treated from June 2000 to December 2001. From October 1998 to May 2000, we consecutively investigated 392 patients with colorectal cancer (CRC) for their detailed family history. The remaining 7 cases were diagnosed on follow-up in the clinic.

Methods

When the probands were verified, we investigated the more detailed family history of patients in the hospital or in the clinic through inquiry by telephone and mail. The tree of each family pedigree was drawn. And these HNPCC patients are being followed up.

RESULTS

Tumor frequency

From October 1998 to May 2000, we investigated 392 patients with CRC for their detailed family history and 10 families with the clinical features of HNPCC were identified, resulting in an overall incidence rate of 2.6 %. The 30 families included 14 Lynch type I families and 16 Lynch type II families. A total of 140 patients developed malignant tumors, 118 (65 males and 53 females) of whom had CRC. The median age at diagnosis of the first colorectal cancer was 45.7 years (range from 20 to 79 years). Eighty-eight patients (74.6 %) developed CRC below 50 years, including 10 patients (8.5 %) under 30 years of age, 56.8 % and 23.4 % of the first colorectal cancers were located in the colon proximal to spleen flexure and in rectum, respectively. Synchronous and metachronous colorectal cancer occurred in 23 (19.5 %) patients.

Extracolonic colorectal cancer

Twenty-seven extracolonic tumors were found, including 10 stomach cancers, 4 endometrial carcinomas, 3 esophageal cancer, 2 hepatic cancers, one renal carcinoma, one pancreatic cancer, one breast cancer, one laryngeal cancer, one lymphoma

and one leukemia. Gastric cancer is the most frequent extracolonic cancer in our series, accounting for 44.5 %.

Pathology of colorectal cancers

We reviewed the HE of 18 cases available. Five (27.8 %) cases of mucinous adenocarcinoma or signet cell type carcinoma were found. Four (22.2 %) tumors had lymphocyte infiltration.

DISCUSSION

Amsterdam criteria I was adopted to diagnose HNPCC in this study. As the widely accepted criteria for diagnosis of HNPCC, the Amsterdam criteria were established by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC). But as clinical criteria, the Amsterdam criteria are too restrictive, thus leading to a number of limitations: (1) The failure to acknowledge the contribution of endometrial cancer and other extracolonic cancer to the HNPCC diagnosis. (2) Small family size or poor documentation of disease and cause of death limits the identification of many affected families[12]. (3) New mutations are not likely to be identified. Estimates of HNPCC frequency varied from country to country. On the one hand, a difference actually exists among different areas, ethnics, nationalities, etc. On the other hand, these studies were not based on uniform criteria. Amsterdam criteria I and II, Japanese criteria and other criteria for suspected HNPCC were used in different studies. According to the Amsterdam criteria, many population-based studies in foreign countries yielded the frequency at 1-10 %. In 1999, a national epidemiological research done in Italy indicated a frequency of HNPCC of 7 %[13]. Nevertheless, suspected HNPCC cases were included in this study. The actual frequency of HNPCC will be lower than 7 % obviously with Amsterdam criteria I. Another study by Peel *et al*. showed that the frequency of HNPCC was nearly 1 %[14]. In China, Bo Zhao reported that HNPCC accounted for 5.2 % of the Chinese population[15]. However, this study included 11 HNPCC families fulfilling Amsterdam criteria I and 5 HNPCC families according to Japanese criteria. The actual frequency of HNPCC was 3.6 % excluding the 5 families fulfilling Japanese criteria. The frequency of HNPCC was found to be 2.6 % in our study, which agrees with previous studies.

To solve this problem, many investigators developed additional criteria, such as the Japanese criteria for HNPCC. They include class A, in which there are three or more colorectal cancers within first-degree relatives, and class B, in which there are two or more colorectal cancers within first degree relatives, and any of the following: (1) early onset of colorectal cancer (age <50years). (2) Right colon involvement, or (3) synchronous or metachronous colorectal and/or extracolonic cancers. Among our 392 patients, 24 families were found according to these criteria, accounting for 6.1 % of the total colorectal cancers. Compared with the Amsterdam criteria, the Japanese criteria are relatively looser, thus increasing the frequency for diagnosis of HNPCC. But there still remain some problems: (1) It does not give enough attention to extracolonic cancer in the diagnosis. (2) The early age of onset and transmissibility of HNPCC, which are the most striking characteristics of HNPCC, have not been emphasized. These weaknesses make it easy to diagnose sporadic colorectal cancers as HNPCC.

In 1998, new selection criteria for collaborative studies, called revised ICG-HNPCC or the Amsterdam criteria II, were proposed by ICG-HNPCC (The classic Amsterdam criteria were kept as Amsterdam criteria I). The new criteria include: (1) There should be at least three relatives with a histologically verified HNPCC-associated cancer (colorectal cancer, cancer of endometrium, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two. (2) At least two successive generations should be affected. (3) At least one should be diagnosed below 50 years of age. The new criteria raised the diagnostic value of some extracolonic cancers. Considering the risk of gastric and hepatic cancers is not high in the relatives, they excluded stomach cancer and hepatic cancer[16], which were the most prevalent cancers in HNPCC families and in the general population of some Asian countries, including China, Korea, etc. The incidence of cancers of endometrium and small bowel is relatively lower than that of western countries. So the Amsterdam criteria II may be more applicable to western countries than to Asian countries. In our 392 consecutive colorectal cancer patients, except for the 10 families fulfilling the criteria I, no families met the Amsterdam criteria II. However, if we included other HNPCC-associated cancers in the criteria, 24 additional families would be found. Including the 10 families for criteria I, they accounted for 8.7 % of the 392 colorectal patients. We think that the specificity and sensitivity of the Amsterdam criteria II are not wholly suitable for the diagnosis of HNPCC in China. We have performed the detection of microsatellite instability, sequence analysis of mismatch repair genes and the detection of hMLH1 and hMSH2 protein on the probands of these 24 kindreds and 18 HNPCC patients. If we can detect the alteration of mismatch repair genes in these HNPCC families, we may include gastric and hepatic cancers in HNPCC related extracolonic tumors. Further epidemiological and genetic studies in China will advance our knowledge on HNPCC. The variance and similarity between Chinese and western countries should be evaluated. It is necessary to establish the Chinese criteria for HNPCC.

HNPCC is a syndrome that affects a distinct percentage of the total colorectal cancer population. It is characterized by the development of cancer at an early age[17-19], predominance of proximal colonic cancer[20-23], excess of multiple cancers[24-27], an increased risk for selected extracolonic adenocarcinomas[28], early occurrence of colonic adenomas[16] and better prognosis[29-31]. *In vitro* experiments showed that HNPCC is resistant to 5-Fluorouracil (5-FU), Cis-diaminedichloroplatinum (DDP) and Nitrogen mustard. By contrast, HNPCC is more sensitive to γrays. Identifying individuals afflicted with HNPCC has implications for early diagnosis, surgical management, chemotherapy, prognosis, follow-up, and surveillance of HNPCC patients and family members at risk. We have noticed that patients with HNPCC inherit a germline mutation in one of the genes responsible for repair of DNA mismatch errors[32,33]. However, given the clinical unavailability for widespread application of gene test and the enormous cost for gene mutation hunting, selection of patients with HNPCC based on suspicious family history is still the most important approach[34-36].

Early age of cancer onset is one of the most striking features about HNPCC. The average age to develop colorectal cancer was 45 years, 20 years earlier than the sporadic colorectal cancer. The study involving 43 HNPCC kindreds and 140 HNPCC patients by Bertario *et al* showed that the average age of onset was 49 years[36]. Bo Zhao *et al* reported the mean age of cancer onset in 16 Chinese HNPCC families, which was 50.8 years in 68 patients[15]. Another 13 HNPCC kindreds in China were reported by Sheng *et al* whose median age at diagnosis was 41 years. In Sheng' s study, 68.75 % of the colorectal cancer developed below age of 50 years, and 90.63 % before 60 years of age[37]. In the present study, the median age of onset of the first colorectal cancer was 45.7 years, with 74.6 % under age of 50 years and 8.5 % under 30 years of age.

Another important clinical characteristic of HNPCC is that the cancer is inclined to be located in the proximal colon. A Swedish national investigation in 2001 demonstrated the proportion of cancers located in the proximal colon was 51 %

of the total[38]. Similar to the other reports, the colorectal cancer is more commonly found proximal to the splenic flexure (58.3 %) in our study. So a relatively young patient, especially younger than 50, with a proximal colon lesion is a clue to be noted. Special attention must be paid while inquiring into the family history. However, there were contrary reports. The percentage of cancers proximal to the splenic flexure was only 25 % in Peel' s research[14]. Given the early age of onset of the cancer and most of the tumor will develop in the proximal colon, we recommend that colonoscopy be performed for the family members with HNPCC and repeated annually or biannually thereafter from the age of 25 years. Flexible sigmoidoscopy is not an effective screening approach in this disease.

HNPCC also predisposes individuals to multiple synchronous and metachrounous colon cancer. The prevalence rate of synchronous and metachrounous colorectal cancer was about 35 %[16]. Peel *et al* reported that 12.5 % of the patients had synchronous and metachrounous cancers in the colon. Although the rate was not high, it was still higher than that of the patients without family cancer history and non-HNPCC cases with positive family cancer history, being 2.6 % and 5.9 % respectively. And the difference was statistically evident (P=0.023)[14]. A domestic investigation in China showed the percentage of synchronous and metachrounous colorectal cancers was 39.5 %. All of them developed within ten years after surgery and needed reoperations[15]. In our series, 23 (19.5 %) of 118 patients presented with multiple cancers in the colorectum. The high incidence of multiple cancers implies that subtotal colectomy is an appropriate management when colon cancers are found in affected patients. It can reduce the chance of developing synchronous colorectal cancer and simplify the endoscopic examination[39]. But considering the effect on the quality of life after subtotal colectomy and the psychological attack on the patients, we usually chose segmental resection for colorectal carcinoma and give intensive follow-up. Only when the patients were diagnosed with multiple cancers or adenomas at other segments, would subtotal colectomy be performed.

Individuals in HNPCC families had an increased risk of developing extracolonic carcinomas including endometrium, stomach, ovary, small intensive, pancreaticobiliary system, upper urological tract, and other sites. Fourteen Lynch type I families and 16 Lynch type II families were found in the 30 HNPCC families (0.88:1). There were 3 Lynch type I families and 13 Lynch type II families in a total of 16 HNPCC kindreds in Bo Zhao' s study(0.23:1)[15]. So extracolonic tumors are frequently seen in HNPCC patients and may contribute to the diagnosis of HNPCC. For this reason, extracolonic cancers were included in the Amsterdam criteria II. According to the reports of western countries, the endometrial and stomach cancers are the first and the second most common tumor in HNPCC, respectively. A study in Portugal revealed that endometrial carcinoma was most frequent in HNPCC extracolonic tumors, the prevalence among women patients even reached 25 %[40]. In our series, of the 81 patients in the 16 Lynch syndrome II families, 27 developed extracolonic carcinomas. The three most common tumors were stomach cancer (12/27), endometrial carcinoma (4/27) and esophageal neoplasm (3/27). Different from the western countries, the incidence of stomach carcinoma was significantly higher than endometrial cancer (P<0.05). Bo Zhao *et al* in China reported 34 cases of extracolonic cancer in 16 HNPCC families. He also found stomach cancer was the most common extracolonic tumor in HNPCC (11 cases of stomach cancers) and endometrial cancer was less common (7 of 34) than gastric cancer[15]. The difference in extracolonic tumor spectrum between China and western countries may lie in many aspects. The small size of our sample may be one of the reasons. Besides, different types of mutation or mutation loci and interaction between environment, life style, ethnics and genotype may also contribute to the observed variation.

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