INTESTINAL POLYPOSIS IN CHILDREN

Intestinalne polipoze u djece

Nada PAVLOVIĆ-ČALIĆ and Kasim MUMINHODŽIĆ

Clinic for Internal Diseases, University Clinical Centre Tuzla,
Bosnia and Herzegovina

Review article

Summary

This is a brief review of Intestinal polyposis in children. Three Intestinal polyposis syndromes are described in some detail, along with procedures for diagnosing and treatment and follow up of patients. In this paper the importance of diagnosing inherited polyposis syndromes is emphasized such as Familial adenomatous polyposis, Peutz- Jeghers syndrome and Juvenile polyposis syndrome. The clinical screening programme should be advised for family members at risk and colectomy in affected individuals for the purpose of reducing the frequency of colorectal cancer.

Key words: Intestinal polyposis ▪ Children ▪ Screening ▪ Management

Revijalni članak

Sažetak

Ovo je kratki revijalni članak na temu intestinalne polipoze u djece. Opisana su tri sindroma intestinalne polipoze, zajedno sa procedurama za njihovu dijagnostiku, tretman i praćenje. U ovom članku je naglašena važnost dijagnostike nasljednih polipoznih sindroma, kao što je familijarna adenomatozna polipoza, Peutz-Jeghersov sindrom i sindrom juvenilne polipoze. Klinički skrining program treba savjetovati za sve rizične članove porodice, dok se za one koji su pogođeni nekim od pomenutih sindroma savjetuje kolektomija, a sve to kako bi se reducirao broj kolorektalnih karcinoma.

Ključne riječi: Intestinalna polipoza ▪ Djeca ▪ Skrining ▪ Menadžment

INTRODUCTION

The first reports of intestinal polyposis appeared in the medical literature in 1861 and 1873. There are inherited polyposis syndromes and non-inherited polyposis syndromes. Inherited polyposis syndromes are: adenomatous polyposis syndromes and hamartomatous polyposis syndromes. The adenomatous

polyposis syndromes include Familial Adenomatous Polyposis and its variant, Gardner syndrome, some Turcot syndrome families, and attenuated adenomatous polyposis coli (AAPC). Hamartomatous polyposis syndromes include Peutz - Jeghers syndrome and Juvenile polyposis (1).

In 1939, Lockart-Mummery demonstrated that prophylactic examination of family members at risk and colectomy in affected individuals reduced the frequency of colorectal cancer. On this basis, the St. Mark's Hospital Polyposis Registry was founded as the first polyposis register in the world (2).

FAMILIAL ADENOMATOUS POLYPOSIS

Epidemiology and Genetics

Familial Adenomatous Polyposis (FAP) is an autosomal dominant condition, and has a prevalence of 1/8 000. Autosomal dominant inheritance means that affected persons are genetically heterozygous, such that each offspring of a patient with FAP has a 50% chance of inheriting the disease gene. Males and females are equally likely to be affected (3, 4).

Most cases of FAP are due to mutations of the APC gene, on chromosome 5q21. Individuals who inherit a mutant APC gene have a very high likelihood of developing colonic adenomas; the risk has been estimated to be over 90%. The loss of APC gene function causes FAP. The clinical form of FAP depends on localisation on the germ line mutation of the APC gene. The serious type is caused by the germ- line mutation of exon 15. Around 10% of families cannot be genetically evaluated, the possible reasons are large intragenic deletions or mutations of the promoter region.

There are three general types of genetic tests: linkage testing, in vitro protein synthesis (IVPS) testing and identification of the specific mutation. In each case DNA is obtained from white cells of peripheral blood. Direct DNA sequencing is then used at gene sites indicated by these methods to determine the precise mutation. If the germline mutation of the APC gene in FAP families is known, it is possible to clearly distinguish between carriers who need to undergo surveillance by regular endoscopies and non-carriers who can be excluded from a surveillance programme. Mutation analysis in large samples of FAP patients has revealed a consistent correlation between the site of mutation in the APC gene and severity of intestinal polyposis or presence of clinically relevant extracolonic features. Patients with mutation at codon 1309 tend to develop adenomas more frequently and at earlier age than patients with other mutations (6).

Clinical Manifestations

Classically, it is characterised by multiple (> 100) adenomatous polyps in the colon and rectum developing after the first decade of life (Figure 1).

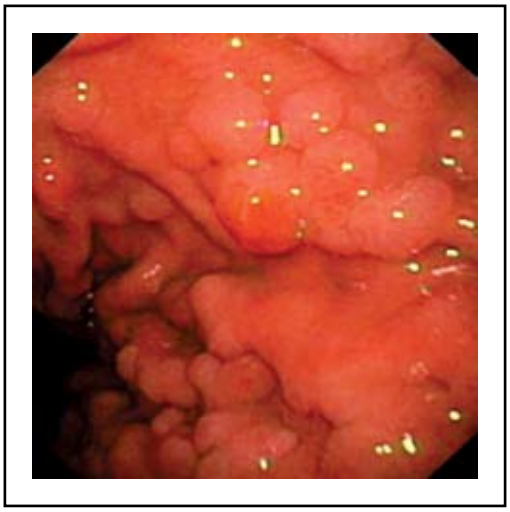

Figure 1 *Familial adenomatous polyposis - endoscopic finding*
Slika 1 *Familijarna adenomatozna polipoza - endoskopski nalaz*

Variant features in addition to the colonic polyps may include polyps in the upper gastrointestinal tract, extraintestinal manifestation such as osteomas and epidermoid cysts, desmoid tumours, congenital hypertrophy of the retinal pigment et epithelium, and other malignant tumors, small bowel cancer, hepatoblastoma, and brain tumors (7).

The age of onset of adenomas in the colon is variable: by age 10, only 15% of FAP gene carriers manifest adenomas, by age 20; the probability rises to 75%; and by age 30, 90% will have presented with FAP. Without any intervention, most persons with FAP will develop colon or rectal cancer by the fourth decade of life. Thus, screening and intervention for at-risk persons has conventionally consisted of annual sigmoidoscopy beginning around puberty. The objective of this regimen is early detection of colonic polyps in those who have FAP, leading to preventive colectomy (8, 9).

Management of a New Patient

In the management of a new patient it is necessary to follow the steps indicated bellow: confirm diagnosis by histopathology, colonoscopy with dye spray, experienced review of pathology blocks if operated elsewhere. Obtain detailed family pedigree through Registry who will notify at risk individuals where possible. Obtain consent for DNA testing, draw blood, monitor processing for use with at risk individuals, arrange consultation with geneticist if requested.

The early appearance of clinical features of FAP and the subsequent recommendations for screening beginning

at puberty raise special considerations relating to the genetic testing of children for susceptibility genes. Some proponents feel that the genetic testing of children for FAP is an example where the possible medical benefit justifies genetic testing in minors, especially for the anticipated 50% of children who will be found not to be mutation carriers and who, thus, can be spared the necessity of unpleasant and costly annual sigmoidoscopy. The psychological impact of such testing is currently under investigation (5, 9).

Treatment of the Large Bowel

The patient must understand the options for treatment. A permanent stoma should not be considered unless there is low rectal cancer, sometimes when there is desmoid disease or when the anal sphincter is weak. In practice the choice lies between: colectomy with ileorectal anastomosis and restorative proctocolectomy. Indications for colectomy with ileorectal anastomosis: young patients (15-25 years old), low density polyposis phenotype (< 1000 polyps overall), low density genotype, <5 rectal polyps, concurrent desmoid disease and palliative operation. Follow up after treatment: 6 monthly flexible sigmoidoscopy and remove polyps > 5 mm or if confluent, and consider chemoprevention with celecobix 400 mg BD or Sulindac 150 mg BD and consider pouch conversion. Indication for restorative proctocolectomy is: older new patient (over 25 years old), conversion of ileorectal anastomosis in patients over 35 years, high density polyposis phenotype (>1000 polyps overall) regardless of age, high density genotype and some patients with rectal cancer. Follow up after treatment: annual flexible examination of pouch. Pouch biopsy, blood tests (particularly B12 and serum folic acid (10, 11).

Management of at Risk Relatives

A detailed history of the family should be obtained and relatives at risk of inheriting FAP identified. These relatives should, where possible, be informed of their risk and offered screening. Those advising the "at risk" relatives should understand the implications and application of advanced predictive DNA testing. They should be qualified to obtain consent for DNA testing and to impart the results. If predictive DNA test is negative, a full explanation of the meaning of this result must be given before the patient can be discharged. If the causative mutation in the family is unknown, entry into a clinical screening programme should be advised. Ideally this would consist of yearly flexible sigmoidoscopy at ages 14, 15, 16, 17, 18 and 19. Five yearly colonoscopy with dye spray by an experienced endoscopist starts age 20 with flexible sigmoidoscopy in the intervening years. This person should not be discharged from the screening programme and should be notified in the event a predictive DNA test becomes available (12).

PEUTZ-JEGHERS SYNDROME

Epidemiology and Genetics

Peutz-Jeghers syndrome is an inherited disorder expressed as intestinal hamartomatous polyposis in association with characteristic mucocutaneous pigmentation. It is a rare syndrome, encountered in polyposis registries in the United states about one tenth as often as FAP. The inheritance is autosomal dominant. Gene mapping studies have identified linkage to a locus on chromosome 19p in each of 12 European families in one study (13).

Clinical Manifestation

The mucocutaneous pigmentation, or melanin spots are a distinctive feature that is observed in more than 95% of affected persons (Fig. 2). Gastrointestinal hamartomatous polyps occur in 88% to 100 % of individuals with Peutz-Jeghers syndrome. They most commonly are present in the small intestine (64-96%) but also frequently occur in the stomach (24-40%) and colon (60%).

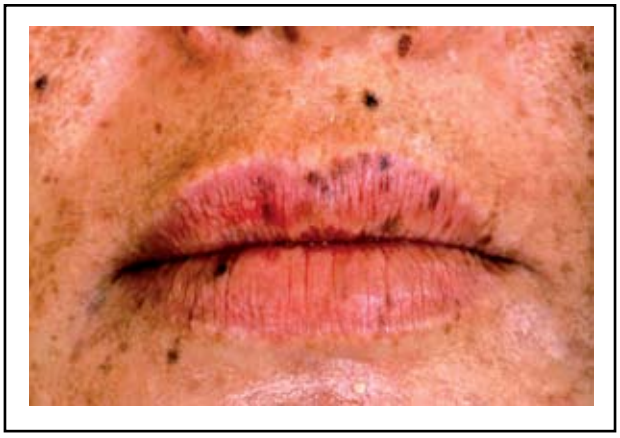

Figure 2 *The melanin spots in the perioral area and on the lips in patient with Peutz-Jeghers syndrome*
Slika 2 *Melaninske mrlje u perioralnom području i usnama u pacijenta sa Peutz-Jeghersovim sindromom*

The number of polyps varies from 1 to 20 per gastrointestinal segment. Polyp growth begins in the first decade of life, but patients typically do not become symptomatic until the second or third decade. Symptoms arise from larger polyps, which may infarct, ulcerate, bleed, and cause intestinal obstruction and intussusception. Adenomatous change and cancer have been documented to occur in Peutz-Jeghers polyps from all areas of the gastrointestinal tract. The incidence of neoplastic change in the polyps is between 3% and 6%. The most common sites of cancer are the stomach

and duodenum. Several extraintestinal tumors, both benign or malignant, also have reported to have an association with Peutz-Jeghers syndrome. These lesions include: breast cancer, adenoma malignum of the cervix, ovarian tumors, tumor of the testis, pancreatic adenocarcinoma. There are two main management problems: avoidance of multiple repeated laparotomies and 50% risk of cancer death (14).

Treatment of Intestinal Polyps

An experienced endoscopist can control the colonic, gastric and duodenal polyps endoscopically. Small bowel polyps need laparotomy which can be assisted by on-table small bowel endoscopy to remove polyps left undetected by external palpation/transllumination (about 30% of polyps have been shown to be missed if on-table small bowel endoscopy is not used, making laparotomy more frequent) (15).

Management of Peutz-Jeghers Syndrome

The St. Mark's Hospital recommendations are: at each consultation ask about recent surgery, new family members, abdominal pain, rectal bleeding and check for jaundice. Recommended investigations are: haemoglobin yearly, endoscopy, top and tail, 3 yearly; barium follow through 3 yearly; breast screening for females as per national screening programme; be alert that any clinical abnormality raises the question of malignancy. For small bowel polyps >1.5 cm, or smaller polyps accompanied by abdominal pain laparotomy and operative enteroscopy are recommended (16).

JUVENILE POLYPOSIS

Epidemiology and Genetics

Juvenile polyposis is a very rare premalignant condition defined by any one of the following: 10 or more juvenile polyps, juvenile polyps through of the gastrointestinal tract; or any number of juvenile polyps in an individual with a family history of juvenile polyposis. Juvenile polyps are nonneoplastic hamartomatous polyps that usually occur in the colons of children between 4 and 14 years of age. One percent to 2% of children express such polyps. In 20% to 50% of juvenile polyposis cases, the condition is familial, with an autosomal dominant pattern of inheritance.

The PTEN gene located at10q23 has been considered a candidate responsible for a variety of hamartomatous polyposis syndromes. Germline mutation of PTEN have now been found in patients with juvenile polyposis. The cumulative risk for colorectal cancer is less than 50% (17).

Clinical Manifestations

The polyps in both the familial and nonfamilial forms of juvenile polyposis are most commonly found in the colon but may occur throughout the intestinal tract.

In the nonfamilial form of polyposis the average age at presentation of symptoms is 4.5 years, and in the familial cases it is 9.5 years. The most common manifestation is rectal bleeding and anemia, which may occur in as many as 75% of patients. Extraintestinal abnormalities occur in some patients and include: patent vitellointestinal duct, gut malrotation, pulmonary AV fistulae, cryptorchidism, cleft palate, mental retardation, hydrocephalus. A few patients have marked gastric polyposis, which can bleed. A study from the St. Mark's Hospital in London found a 15% incidence of colorectal cancer in patients under 35 years, and carcinomatous and adenomatous changes are found in the patients with familial or nonfamilial juvenile polyps (18, 19).

Management

It would seem prudent periodically to screen children of a parent with the familial form of juvenile polyposis. Screening should begin after 12 years of age if symptoms have not already led to a diagnosis. Asymptomatic adult relatives should be screened because of their increased risk of cancer.

An experienced endoscopist can often control the colonic, gastric and duodenal polyps. Colectomy and even gastrectomy may be necessary in severe cases. Laparotomy may be indicated if polyps develop in the jejunum, although this is rare. Most care is individualised to the circumstances, evidence and experience being limited.

Follow up: regular colonoscopy, one to three yearly in patients where colonoscopic clearance of polyps is possible. Regular oesophageal gastroduodenoscopy, one to five yearly depending on the extent of upper gastrointestinal disease. Extra-intestinal abnormalities of clinical significance should be managed appropriately (20).

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Kontakt adresa autora: doc. Dr. Nada Pavlović – Čalić, Klinika za Interne bolesti
JZU UKC Tuzla, Trnovac bb, 75000 Tuzla; Tel.:+387 (35) 303 302; email: nada.pavlovic-calic@ukctuzla.ba