Colorectal cancer in the course of familial adenomatous polyposis: natural history and treatment methods

Rak jelita grubego w przebiegu rodzinnej polipowatości, naturalny przebieg choroby i metody jej leczenia

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Słowa kluczowe: rak jelita grubego, rodzinna polipowatość gruczołakowata, mutacja genu APC, polipowatość jelita grubego.

Abstract

Familial adenomatous polyposis (FAP) is a group of diseases, mostly caused by an APC suppressor gene mutation inherited in an autosomal dominant pattern. It results in numerous adenomas formed in the epithelium of the large intestine leading to colorectal cancer in 100% of cases, with the mean age of 39, and a high risk of other fatal neoplasms. There is no causative treatment possible. Total colectomy performed at the right time is the only way to prevent the individual from developing colorectal cancer. The aim of this study was to present the diagnostic performance and treatment methods of FAP. Fast diagnosis and strict surveillance of patients and their families are the most important for effective treatment.

Streszczenie

Rodzinna polipowatość gruczołakowata (FAP) to heterogenna grupa chorób genetycznych związanych z polipowatością jelita grubego. Najczęściej jest dziedziczona autosomalnie dominująco, a mutacja dotyczy genu supresorowego APC. W błonie śluzowej jelita grubego chorych rozwijają się setki polipów gruczołakowatyń, o wysokim potencjale nowotworzeni. Ryzyko wystąpienia raka jelita grubego na ich podłożu wynosi 100%, a średni wiek jego rozwoju to 39 lat. Zespół ten predysponuje również do innych, łagodnych i złośliwych nowotworów. Obecnie nie jest znane leczenie przyczynowe tej choroby. Cel pracy było przypomnienie zasad nadzoru endoskopowego i leczenia FAP. Wcześniej postawiona diagnoza, ścisły nadzór nad pacjentem i jego rodziną są najważniejsze dla uzyskania zadowalających efektów leczenia.

Introduction

Familial adenomatous polyposis (FAP) is an inherited syndrome, characterised mostly by omnipresent polyps located in the colon and rectum. These lesions are related to mutations in the APC and MYH genes and present a high cancerogenic potential. Moreover, the syndrome predisposes to various types of malignant and benign neoplasms located in the small intestine, stomach, pancreas and retroperitoneal space [1]. It is estimated that 1% of colorectal cancers worldwide develop on the background of familial adenomatous polyposis, but for individuals with FAP the lifetime risk of colorectal cancer (CRC) is 100%. Cancer of the colon and rectum is the third most frequent cancer in males worldwide (660,000 cases, 10%), and the second in females (570,000 cases, 9%). Nearly 60% of onsets are observed in well-developed countries [2]. The population risk of colorectal cancer (CRC) is high and it is estimated at the level of 5–6% [3]. Among patients with colorectal cancer aged under 40 in the Danish population, the percentage of FAP was 5% [4]. The 5-year survival rate depends on the clinical stage by establishing a diagnosis and is as follows: stage I – 70%, stage II – 63%, stage III – 46% and stage IV– 12% [5]. CRC is the second most frequent cancer-related cause
of death worldwide; according to the WHO in 2018 it caused 862,000 deaths (8% of cancer-related deaths). Morbidity of this cancer in Poland and worldwide continues to increase.

The objective of the study is to review current diagnostic methods, surveillance and treatment methods in FAP according to evidence-based medicine.

**Molecular biology of FAP**

Familial adenomatous polyposis (FAP) is a hereditary syndrome which develops mainly on the background of APC suppressor gene mutation. The APC gene is located on chromosome 5, region q21; it consists of 8535 base pairs divided into 15 exons [1]. Its product, APC protein, participates in the processes of normal epithelium formation, ensures integrity of the cytoskeleton through the actin complex [6], controls inhibition of cell proliferation by way of apoptosis, promotes cell adhesion through the β-catenin complex and allows migration of intestinal cells from crypts up to the intestinal lumen [7]. Normal APC protein inhibits proliferation of the damaged cells and directs them to the route of controlled death in the mechanism of apoptosis. Its dysfunction leads to accumulation of mutations in the genetic material, excessive cell proliferation and consequently to malignancies [8]. Another function of APC protein is promoting the migration of the intestinal epithelial cells through the kinesin complex KAP3. Young cells of the intestinal epithelium, which are formed from matrix cells at the crypt base, subsequently migrate upward towards the intestinal lumen where they form a layer. During the migration they undergo differentiation into individual types of intestinal epithelium cells, i.e. structural, cube-like, and secretory. Expression of the wild-type APC gene is mandatory for the normal course of this process. Its malfunction, which is caused by impaired structure due to genetic mutation, inhibits the migration of epithelial cells which causes their accumulation inside crypts and development of polyps [7]. The role of the APC protein is best understood in carcinogenesis of the mucous membrane of the large intestine.

Familial adenomatous polyposis is mainly (over 95%) inherited, in an autosomal dominant pattern, and penetration of the gene is approximately 95%. This means that each child of an affected person has 50% chance of inheriting the mutation [7]. There are no healthy carriers, so each person who inherits the impaired gene becomes instantly ill. 20–40% of patients with FAP have a negative family history [6]. It is considered that even 20% of mutations in the APC gene are formed de novo (1 per 8,000–10,000 births) [6, 9, 10] mostly in the mechanism of loss of heterozygosity. In these patients the diagnosis is usually late, when symptoms and signs of colorectal cancer have already developed [6, 11].

**Clinical biology of FAP**

Clinically familial adenomatous polyposis syndrome is manifested by the presence of numerous (from several to more than several thousand) adenomatous polyps in the large intestine, most frequently with tubular architecture, more rarely villous. They typically start to form during the period of puberty, median approx. at the age of 16 [12] (although cases of their early burden were described at the age of even 2–3). In the natural course of the disease multiple polyps are located in the mucous membrane of the whole large intestine and they express high potential for carcinogenesis. The mean age of CRC onset in FAP is 39 and the mean age of death is 42 [12, 13]. The lifetime risk of developing colorectal cancer in this condition is 100% and the lesion is in as many as 50% of cases multifocal when diagnosed [5]. Only in approximately 8% of individuals does the disease have a mild and non-typical course [13].

The FAP syndrome predisposes to variety of other benign and malignant neoplasms, including thyroid cancer (2–3%), fetal hepatoblastoma (approx. 1%), brain tumours (< 1%), duodenal and gastric cancer. Other clinical manifestations of FAP are congenital hypertrophy of the retinal pigmented epithelium (CHRPE), which occurs in 70–80% of individuals, epidermoid cysts in 50%, osteomas in 50–90%, gastric and duodenal adenomas. In addition, desmoid tumours, supernumerary teeth, and adrenal adenomas are observed [13]. It was confirmed that duodenal adenomas may occur in as many as 50–90% of patients with FAP [13–15]. The prevalence of duodenal cancer in this group is 1–6%, and the mean age of establishing a diagnosis is 47 [12]. It is a frequent cause of death in patients with familial adenomatous polyposis [12, 16]. According to some researchers, it is the most frequent cause of death among patients with FAP after colectomy [12, 17].

**Establishing a diagnosis**

Establishing a diagnosis of FAP is based on confirmed presence of > 100 of polyps in the large intestine. In individuals with fewer polyps, a typical family history, typical course of the disease and presence of extracolonic manifestations are taken into consideration.

Every person with a clinical manifestation or family history of FAP should undergo genetic testing.

**Genetic testing**

According to the American Gastroenterology College of Gastroenterology Guideline (2015) genetic testing should be performed in individuals who have:

- a history of more than 10 accumulative adenomas in the colon and/or rectum,
- a family history of one of the intestinal polyposis syndromes,
• a history of adenomas of colon and/or rectum and symptoms of typical extracolonic manifestations such as adenomas in the duodenum, desmoid tumours, CHRPE, epidermal cysts, osteomas [18].

Table 1. Spiegelman’s classification

<table>
<thead>
<tr>
<th>Points</th>
<th>No. of polyps</th>
<th>Size of polyps [mm]</th>
<th>Histology</th>
<th>Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1–4</td>
<td>1–4</td>
<td>Tubular/hyperplastic/inflammatory</td>
<td>Mild*</td>
</tr>
<tr>
<td>2</td>
<td>5–20</td>
<td>5–10</td>
<td>Tubulovillous</td>
<td>Moderate*</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 20</td>
<td>&gt; 10</td>
<td>Villous</td>
<td>Considerable^</td>
</tr>
</tbody>
</table>

Interpretation: Grade 0: no points; Grade I: 1–4 points; Grade II: 5–6 points; Grade III: 7–8 points; Grade IV: 9–12 points. *According to the present classification means low grade dysplasia. ^According to the present classification means high grade dysplasia [13].

Table 2. The recommended scheme of maintaining strict endoscopic surveillance of duodenum management

<table>
<thead>
<tr>
<th>Grade according to Spiegelman</th>
<th>Time between successive examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/I</td>
<td>5 years</td>
</tr>
<tr>
<td>II</td>
<td>3 years</td>
</tr>
<tr>
<td>III</td>
<td>1–2 years</td>
</tr>
<tr>
<td>IV</td>
<td>Consider surgery</td>
</tr>
</tbody>
</table>


Surveillance

Spiegelman et al. created a classification of duodenal polyps according to their number, size and histological type, which qualifies patients into groups at low, mediocre and high risk of malignant transformation of adenomas (Table 1).

A group of experts have established a scheme of surveillance of the duodenum for patients with familial adenomatous polyposis, based on this classification. The recommended scheme of maintaining strict endoscopic surveillance of duodenum management was presented in Table 2.

Extraduodenal polyps of the small intestine are also frequent in FAP. The prevalence is estimated at 50% for the jejunum, and 20% for the ileum. However, low prevalence of small intestine cancer in patients reveals a low potential of carcinogenesis in this localization [19, 20]. Another concern in patients with FAP are desmoid tumours [21]. These are histologically benign fibrous tumours, which are most often formed spontaneously in the retroperitoneal space and as an iatrogenic condition after surgical interventions in the peritoneal cavity [12, 22]. Two clinical studies revealed that the mean time between colectomy and the diagnosis of desmoid tumours was 5 years [21, 23]. The prevalence of desmoid tumours in FAP is approximately 20% [21]. They are a common cause of death among patients suffering from this condition due to limited possibilities and poor effects of available treatment methods. And more another problematic issue – thyroid cancer – occurs more often in females than males. Systematic examinations of thyroid gland are recommended [24] in FAP syndrome, but they are not performed routinely [20].

Attenuated FAP (AFAP) is a milder form of FAP, where the number of polyps in the large intestine usually does not exceed 100, and they are located more proximally in the colon affecting mostly its right side. In the natural course of the disease the mean age of developing CRC is 56 years [20]. The exact criteria of standing a diagnosis of AFAP have not been finally established. In 2007 there was a meeting of experts concerning this problem, where two main suggestions for criteria of diagnosis were presented [19].

Nielsen’s criteria [19]:
1) at least 2 family members aged over 30 with 10–99 polyps, and lack of a family member aged under 30 with > 100 polyps;
2) 1 person > 30 with 10–99 polyps and a first-degree relative with a small number of polyps and CRC, lack of family member aged < 30 with > 100 polyps. Criteria by Knudsen et al. [19]:
1) dominant inheritance;
2) 3–99 polyps of the large intestine in a person aged ≥ 20.

Strict endoscopic surveillance of patients with FAP should be carried out in the form of fibrosigmoidoscopy from the age of 10–12 every 2 years until the diagnosis of adenomas, and subsequently, annually until planned colectomy [19, 24, 25].

Patients with atypical form of FAP should have full colonoscopy performed from the age of 18–20 every 2 years, and after diagnosis of the polyps, annually [19]. In the case of symptomatic individuals, the screening should be undertaken earlier. There is no age limit from which it is recommended to perform endoscopic examinations [19]. It is significant that the strict surveillance and following of recommendations enables the correct treatment and is associated with a lower mortality rate [19].

Treatment

The treatment of choice both in FAP and AFAP is surgical resection of the large intestine before the malignant transformation of polyps begins. The majority of individuals undergo surgery between the age of
15 and 25 but direct indications and timing for surgical procedure are established individually during endoscopic surveillance [19]. Experts recommend resection of the large intestine when diagnosing a considerable number of adenomatous polyps of the diameter > 5 mm including adenomas with high grade dysplasia [19]. The method is selected individually [24] and is based primarily on the patient's preferences with consideration of general condition, comorbidities, age, gender, reproductive plans and the number of polyps in the rectum [19].

There are three recommended methods of colectomy in FAP:

1) total colectomy with ileorectal anastomosis – IRA;
2) proctocolectomy with ileal pouch-anal anastomosis – IPAA;
3) proctocolectomy with ileostomy.

The third method – proctocolectomy with end ileostomy – is generally not accepted by patients due to worse quality of life and various problems concerning individuals with stoma [26]. It is a method of choice in patients with diagnosed rectal or anal cancer and with anal sphincter disorders. The other indications can include high risk of anal and rectal cancer, severe comorbidities and a desmoid mesenteric tumour rendering forming a pouch impossible [27].

IRA as a single stage procedure is easier to perform than IPAA. It is recommended in individuals with a low number of rectal polyps – with AFAP or so-called ‘mild’ FAP genotype – associated with a lower number of polyps in the rectum and a lower risk of their malignancy and also in young women who are planning to be pregnant. Nevertheless, the 5-year risk of colorectal cancer located in the rectum is high after performing this surgery [12, 13, 19] and ranges from 60 to 78 % [28–30]. The procedure should not be performed in patients with sphincter dysfunctions, colon or rectum cancer and presence of adenomas > 3 cm with severe dysplasia in the rectum [27].

IPAA is a method of total colectomy including the rectum, followed by forming a reservoir of the stapled or sutured ileal loops. Some authorities recommend it as a two-stage procedure – initially requiring the formation of a protective loop ileostomy, which is closed not earlier than after several weeks or months. There are two available methods of performing it – one is traditional handsewn ileal pouch formation which is accompanied by total mucosectomy above the dentate line in which the mucous membrane of the large intestine is totally removed while the continuity of the gastrointestinal tract and the function of sphincters are maintained. The second method – stapled mechanical anastomosis and pouch formation – was brought by technological progress. The method is faster, easier to perform and makes it possible to maintain better anal function as it requires less manipulation of sphincters and a little rectal cuff is left above the anastomosis. Another advantage of a stapled anastomosis is the possibility to perform it with a laparoscopic approach. It is worth laying emphasis on the fact that patients are often young people undergoing preventative surgery. As doctors we should not only be concerned about their life expectancy, but also the quality of their life, which includes their appearance, sexual functions and fertility. The laparoscopic approach promotes a reduced number of abdominal and pelvic adhesions, a lower infertility rate in women than a classical IPAA, and of course avoids large surgical incisions [30]. However, a stapled ileal pouch is related to higher adenoma incidence and higher rectal cancer risk than a hand-sewn pouch [27] as the rectal mucous membrane is preserved. A hot debate over the pros and cons of different methods is continued by authorities. Comparing the two surgical methods, IPAA is associated with a larger number of serious surgical complications than IRA – both early, such as anastomotic leaks, pelvic sepsis or bleeding, and late, such as pouchitis, fistulas or further polyps forming in the pouch and consequently cancer in the pouch [5, 13, 31]. It is important to know that colectomy and formation of the ileal pouch do not cure the disease. Strict endoscopic surveillance still has to be performed, as the ileal mucosa of the pouch develops chronic inflammation, villous atrophy, colonic metaplasia and further polyp formation. Dysplasia is rare in these polyps, although invasive colorectal cancer can still develop [32]. According to recent studies the risk of adenoma burden in the ileal pouch was 7%, 35%, 75% respectively for 5-, 10-, 15-year follow-up [33]. Some studies revealed that up to 18% of patients can develop advanced histological features including metaplastic adenomas and adenocarcinomas [33]. Other concerns in forming a pouch are postoperative adhesions and hypogastric nerve neuropaxia during pelvic dissection, which are believed to be a cause of sexual dysfunctions and infertility in women [31]. IPAA is the method of choice in individuals with a larger number of polyps in the rectum, e.g. more than 15–20 [13], and of so-called ‘bad genotypes’, where polyps in the rectum are not yet present, but the risk of their burden is high. Aziz et al. published a meta-analysis of 12 studies including a total of 1,002 patients with FAP [34] who had undergone IRA or IPAA procedures, and compared the functional effects and the quality of life. It was found that the number of stools per day, defecations at night, and number of pads used in faecal incontinence were significantly lower in the group of patients after IRA. In addition, bowel urgencies more frequently concerned patients after IPAA. They were also more often subjected to re-operation within 30 days. Similar numbers of sexual dysfunctions, dietetic limitations, and post-surgical complications were described after IPAA and IRA [13]. The lifetime risk of colorectal cancer after IRA was estimated at 5%, but a further removal of the rectum was performed in 28% after IRA and 3% after
1. There is an ongoing II Phase of trial by Mayo Clinic. “Erlotinib Hydrochloride in Reducing Duodenal Polyp Burden in Patients With Familial Adenomatous Polyposis at Risk of Developing Colon Cancer” [41].

2. In August 2016 Burke et al. published in BMC Gastroenterology “Efficacy and safety of efalorine sulindac combination therapy versus each as monotherapy in patients with familial adenomatous polyposis (FAP): design and rationale of a randomized, double-blind, Phase III trial” The end of the trial was planned for 2019 and is not finished yet [41].

According to the source in a clinical trial, this combination (compared with placebo) reduced the 3-year incidence of subsequent high-risk adenomas by >90% [42, 43].

**Different forms of familial polyposis coli**

Apart from the classic familial adenomatous polyposis, various forms of it are described. These are: the above-mentioned AFAP syndrome – with a lower severity of the disease, a lower number of polyps in the large intestine, and the later onset of cancer than in the classic form. The MUTYH syndrome inherited in an autosomal recessive pattern – the mutation concerns the MYH gene, whose product is responsible for oxidative DNA damage repair [20]. The defect leads to cell malignancy due to improper DNA repair and accumulation of incidental mutations in the genetic material; the onset of clinical symptoms is estimated at the 4th to 5th decade of life and the development of colorectal cancer usually before the age of 60.

Gardner syndrome – the mutation also concerns the APC gene, more rarely the RAS gene on chromosome 12, and the P53 gene. Apart from typical symptoms of familial adenomatous polyposis, inevitably leading to malignancies, severe disorders in the structure of connective tissue are described. Non-intestinal symptoms include sebaceous adenomas on the skin, osteomas, supernumerary teeth, odontomas, and other tumours derived from the connective tissue.

Turcot syndrome – a mutation in the APC gene and its typical symptoms are accompanied by medulloblastomas (autosomal dominant form), and multi-form glioblastomas (recessive form).

In Poland, the Register of Patients with Familial Adenomatous Polyposis has been kept since 1989 by Prof. Krokowicz in Poznan. He closely cooperates with the Department of Genetics at the Pomeranian Medical University, and the Institute of Human Genetics, Polish Academy of Sciences in Poznan, where the DNA bank for patients with FAP and their families is located. The DNA Bank for Polish patients with familial adenomatous polyposis contains material from nearly 400 families [8].

**Conclusions**

In the natural course FAP inevitably leads to early onset of colorectal cancer, often metastatic and mul-
tifocal when diagnosed, with poor clinical outcomes. Causative treatment of this condition is not yet pos-
sible. The surgical removal of the colon and rectum remains the only way to prevent CRC. An aware and watchful physician is a core element in the process of establishing a fast diagnosis and processing a proper life-saving treatment.

**Conflict of interest**

The authors declare no conflict of interest.

**References**

11. Rustin RB, Jagelman DG, McGannon E, Fazio VW, Laverty IC, Weakley FL. Spontaneous mutation in familial ad-
16. Domizio P, Talbot IC, Spigelman AD, Williams CB, Phillips RK. Upper gastrointestinal pathology in familial ad-
22. Durno CA, Gallinger S. Genetic predisposition to colorec-
23. Sagar PM, Moslein G, Dozois RR. Management of des-
moid tumors in patients after ileal pouch-anal anastomo-
24. Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kala-
dy MF, Lau MWY, Lu KH, Roach N, Limburg PJ; American Society of Clinical Oncology; European Society of Clini-
28. Bülow S, Vanen H, Jarvinen H, Bjork J, Bisgaard ML, Bü-
low S. Ileorectal anastomosis is appropriate for a subset of patients with familial adenomatous polyposis. Gut 2003; 41: 1350-1355.
29. Heiskanen I, Jarvinen HJ. Fate of the rectal stump after ileal pouch-anal anasto-

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