Familial adenomatous polyposis in children

Rodzinna polipowatość gruczolakowata u dzieci

INTRODUCTION

Familial adenomatous polyposis (FAP) is a rare autosomal dominant syndrome characterized by the presence of hundreds of gastrointestinal, adenomatous polyps which can develop to colon cancer at early age. FAP is caused by an inactivating mutation in the tumor suppressor gene called adenomatous polyposis coli (APC) gene. At early age symptoms may be absent, but with the development of polyps symptoms may occur. Characteristic for FAP is a large number of polyps (over 100), which usually appear in the second decade of life (1). There are multiple related conditions caused by mutation in APC gene and MUTYH-associated polyposis (MAP) which has similar clinical manifestation. Risk of malignancy in patients with FAP reaches 100%, that is why careful and standardized surgical management of FAP is required in order to prevent patients from developing malignancies. In the absence of Polish guidelines for the management of familial adenomatous polyposis Polish doctors should consider using Clinical Practice Guidelines on Familial risk-colorectal cancer published in 2013 by European Society for Medical Oncology.

S t r e s z c z e n i e

Rodzinna polipowatość gruczolakowata (FAP) to najczęstszy dziedziczony zespół polipowatości powodowany przez mutacje antyonkogenu APC (ang. adenomatous polyposis coli gene). Mutacje te prowadzą do powstawania nieprawidłowych białek odpowiedzialnych za tworzenie setek polipów gruczolakowatych umiejscowionych w przewodzie pokarmowym, głównie w jelitach grubych, z których nieuchronnie rozwinię się rak jelita grubego. Istnieje kilka wariantów FAP, między innymi poronna postać FAP (AFAP), także powodowana przez mutacje w genie APC, która charakteryzuje się mniejszą ilością polipów oraz późniejszym ich rozwojem w porównaniu z klasycznym FAP. Występuje również rodzinná polipowatość gruczolakowata występująca przez mutację autosomalnie recezywną występującą w genie MUTYH zwana MAP (MUTYH-associated polyposis), której przebieg jest podobny do AFAP. Ryzyko rozwoju złośliwego raka jelita grubego na podłożu gruczolaków jelita grubego sięga niemal 100%, dlatego tak istotny jest uważny i ujednolicony sposób opieki nad pacjentami z FAP. Ze względu na brak polskich wytycznych dotyczących postępowania w przypadku rodzinné polipowatości gruczolakowatej polscy klinicyści powinni rozważyć wykorzystanie wytycznych opublikowanych przez European Society for Medical Oncology w 2013 roku.
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**Epidemiology**

FAP is the most common inherited polyposis syndrome and occurs in approximately 1:5000 to 1:17,000 (2). The disease occurs de novo with the frequency of somewhere between 1 in 8000 to 1 in 10,000 (3). Among all colorectal cancer FAP make up less than 1% (4).

**Diagnosis**

To diagnose FAP more than 100 adenomas must be identified in colorectum. Typical for attenuated FAP (AFAP), the milder form of FAP, is the lower number of adenomas and later onset of the disease. Clinical manifestation of MUTYH-associated polyposis (MAP) is very similar to APC-associated AFAP.

**Genetics**

FAP is caused by mutation in the tumor suppressor gene called adenomatous polyposis coli (APC) gene. APC is located on chromosome 5 in the q21 region and contains 21 exons (5). Mutations in the APC gene are present in 80-90% of patients with FAP (6). In the remaining patients, FAP results from the occurrence of a de novo mutation in the APC gene. The APC gene is responsible for controlling β-catenin. When APC gene loss it’s function, β-catenin is active and causes cellular proliferation (7). It leads to increased probability of mutations and accumulation of changes in genetic material. If this occurs, abnormal cells may accumulate and develop into polyps and colon cancer. In case of the recessive form of adenomatous polyposis, known as MYH adenomatous polyposis (MAP) there is mutation in MUTYH gene (fig. 1) (8).

**Signs and Symptoms**

The majority of pediatric patients with FAP are asymptomatic and undergo evaluation based on their family history (10). At average age of 15 years of age polyps start to develop (11), but at this time symptoms are rare. First signs of FAP occur as polyps start to grow and multiply (tab. 1). It is not safe to wait for symptoms, because it is usually connected with malignant condition. However there have been reported patients who were 5 years old when polyps were diagnosed (12).

**Tab. 1. Symptoms of FAP**

<table>
<thead>
<tr>
<th>Typical</th>
<th>When the disease is advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood in the stool</td>
<td>Continued weight loss</td>
</tr>
<tr>
<td>Thin stools</td>
<td>Continued lack of energy</td>
</tr>
<tr>
<td>Diarrhea and/or constipation</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, cramping, or bloating</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1. Algorithm for genetic diagnosis in polyposis syndromes (9)**

![Algorithm for genetic diagnosis in polyposis syndromes](image)
There are also such extra-colonic features of FAP present as (tab. 2):
- congenital hypertrophy of the retinal pigment epithelium – CHRPE. CHRPE has been reported to occur in over 50% of the carriers of the mutation in the APC gene (13). It is one of the commonest and earliest extra intestinal manifestations, it lends itself as a screening tool for family members of FAP patients. However the development of molecular biology techniques as well as incomplete penetrance has reduced its significance (14).
- polyps in upper segments of the gastrointestinal tract particularly in stomach and duodenum. Polyps can occur in form of fundus gland polyps or adenomas (15). Stomach polyps occur in approximately 50% of FAP patients and do not have a high potential to form neoplasms. 33% even to 80% of patient with FAP are diagnosed with duodenal polyps (16-18). Polyps located in the ampulla of Vater and the periampullary area can develop into malignant lesion in 4 to 12% of FAP cases (19). The risk of carcinoma is greater in ampullary compared with nonampullary adenomas and increases with the size of adenoma (20),
- dental changes.

Tab. 2. Extra-intestinal features in familial adenomatous polyposis

<table>
<thead>
<tr>
<th>Benign lesions</th>
<th>Malignant lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hypertrophy of the retinal pigmented epithelium</td>
<td>Duodenal and periampullary adenocarcinoma</td>
</tr>
<tr>
<td>Epidermoid cysts</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>Osteoma</td>
<td>Brain tumour</td>
</tr>
<tr>
<td>Desmoid tumour</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>Supernumerary teeth</td>
<td></td>
</tr>
<tr>
<td>Adrenal gland adenomas</td>
<td></td>
</tr>
</tbody>
</table>

Supernumerary teeth as well as osteomas and changes in tooth structure:
- desmoid tumours. In about 10% FAP patients non-cancerous tumors most often found in the abdomen are observed (21). It is also proven that desmoid tumours occur 3 times less frequently in men with FAP than in women (22),
- adrenal masses, a benign tumors in adrenal glands,
- osteomas on the skull and jaw and epidermoid cysts – Gardner syndrome.

Patients with FAP have slightly increased risk of malignancies as compared to individuals without FAP:
- duodenal and periampullary adenocarcinomas,
- thyroid cancers are observed in 1% of patients. More than 94% of cases is diagnosed in women (23, 24),
- central nervous system neoplasms (medulloblastoma) occur with low frequency of about 1% and they are usually gliomas. The occurrence of these tumors together with FAP symptoms in the intestine is described as Turcot’s syndrome (25-27),
- hepatoblastomas are rare neoplasms occurring in children. Increased risk of occurrence of these cancers in APC mutation carriers were observed but the incidence did not exceed 1% (28, 29). However it is recommended to check α-fetoprotein levels and hepatic ultrasounds from birth to 5 years of age.

CANCER RISKS

Patient with FAP who are not diagnosed and treated will develop colon cancer. The average age of malignant transformation diagnosis in untreated patients is 39 years (age 34 to 43 years). Colon cancer occurs by age 20 years in 7%, and by age 25 years in 15% of patients. Extra intestinal malignancies are listed above.

RELATED CONDITIONS

Mutations in the APC gene can cause three related conditions. These conditions are now considered to be variants of familial adenomatous polyposis. These include:
- Gardner syndrome – characterized by the presence of multiple gastrointestinal polyps, osteomas and soft tissue growths (including epidermal cysts, fibromas and desmoid tumors) (30),
- Turcot syndrome – associated with the presence of gastrointestinal polyps and a central nervous system tumor (medulloblastoma) (31),
- attenuated FAP (AFAP) – characterized by fewer polyps (average of about 30 polyps) and delayed onset of colon cancer compared to classic FAP (32).

Researchers recently identified another hereditary form of adenomatous polyposis, MYH-associated polyposis (MAP). Map is caused by a mutation in the MUTYH (also called MYH) gene and is inherited in an autosomal recessive manner. Patients with this disease have fewer polyps (~30) in their colon or rectum than patients with FAP.

Characteristic for MAP is the later age of onset of adenomas and colorectal cancer. Duodenal polyposis seems to be quite frequent and sometimes severe, extraintestinal manifestations such as CHRPE, osteomas and dental anomalies are rarely observed (33).

If any APC pathogenic variant is not identified in patient with colonic polyposis, molecular genetic testing of MUTYH should be considered (34).

Some groups have reported an increased risk to develop other malignancies that are not typically associated with FAP, including ovarian cancer, bladder cancer, and possibly breast and endometrial cancer. However, the risk to develop these cancers has not been well-characterized for individuals with MAP (35, 36).

MEDICAL MANAGEMENT AND TREATMENT

There are no Polish guidelines for the clinical management of familial adenomatous polyposis. In 2013 Eu-
European Society for Medical Oncology has published Clinical Practice Guidelines on Familial risk-colorectal cancer (37).

**APC-ASSOCIATED FAMILIAL ADENOMATOUS POLYPOSIS (FAP AND AFAP)**

**Screening**

Gene testing allows carrying out the most cost-effective screening by driving colorectal examinations to gene carriers. However, when the causative mutation is not identified, all at-risk family members should undergo colorectal screening.

In families with classic FAP, flexible sigmoidoscopy is an adequate technique because of the almost universal distribution of adenomas. This examination should be carried out every 2 years, starting at the age of 12-14 years and be continued lifelong in mutation carriers.

In at-risk individuals from families without an identified APC mutation, surveillance should be carried out every 2 years until age 40, every 3-5 years between 40-50 years, and may be discontinued at age 50 if no polyposis has developed. Once adenomas are detected, colonoscopy should be carried out annually until colectomy is planned [III, A] (tab. 3).

In AFAP cases, since adenomas can be localized in the right colon, colonoscopy is recommended instead of sigmoidoscopy. In this setting, examination should be carried out every 2 years until polyposis is diagnosed. Screening should start at the age of 18-20 years and continue lifelong because of the more heterogeneous penetrance of AFAP. Again, once adenomas are detected, colonoscopy should be carried out annually [III, B] (tab. 3).

Screening for extracolonic manifestations should start when colorectal polyposis is diagnosed or at the age of 25-30 years, whichever comes first.

Gastroduodenal endoscopy using both front and side-view scopes, with special attention to the papillary area, should be carried out every 5 years until adenomas are detected [III, B] (38). Although high-resolution endoscopy, chromoendoscopy or narrow band imaging improve the quality of endoscopic imaging, the benefit of adding these techniques for the evaluation of duodenal adenomatosis is uncertain [IV, C] (39). Since gastrointestinal adenomas may also develop in the jejunum and ileum, it has been suggested to carry out regular screening by barium contrast series or wireless capsule endoscopy [IV, C]. Screening for thyroid cancer should be carried out with annual cervical ultrasonography [IV, C]. Development of desmoid tumours is mainly related to a positive family history and abdominal surgery. In this setting, regular physical examination and abdominal computed tomography (CT) or magnetic resonance imaging (MRI) should be carried out [IV, B]. Screening for other extracolonic manifestations is not justified because of their low prevalence and/or limited clinical impact.

**Tab. 3. Surveillance. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America US Public Health Service Grading System)**

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</td>
<td>A. Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>II. Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
<td>B. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>III. Prospective cohort studies</td>
<td>C. Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs...), optional</td>
</tr>
<tr>
<td>IV. Retrospective cohort studies or case-control studies</td>
<td>D. Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>V. Studies without control group, case reports, experts opinions</td>
<td>E. Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>

**Treatment**

The goal of colorectal therapy is to prevent CRC and includes both endoscopic polypectomy and surgery. Whereas surgical resection is the standard of care in patients with classical FAP, the former can be considered in some patients with AFAP. Most patients with classical FAP undergo surgery between the age of 15 and 25 years.

Surgical resection includes both proctocolectomy with ileal pouch-anal anastomosis (IPAA) and total colectomy with ileorectal anastomosis (IRA). IRA is a relatively simple and straightforward operation, compared with IPAA. The complication rate is low, and the bowel function after surgery is usually good. For IPAA, more extensive surgery is needed (including pelvis dissection), causing reduction of fertility and worse bowel function. The decision on the type of surgery depends on many factors including age, severity of polyposis (i.e. involvement of the rectum), risk of developing desmoids, the wish to have children and the site of the mutation. When a diffuse distribution or severe phenotype is present, IPAA is recommended. On the contrary, when no or only scarce adenomas are detected in the rectum and a mild familial phenotype is observed, including AFAP, total colectomy with IRA can be carried out. Because of the need of endoscopic surveillance of the rectum in the latter context, proctocolectomy should be considered in patients reluctant to undergo regular follow-up [III, B].

Duodenal adenomas are usually managed with endoscopic polypectomy based on the Spigelman stage (tab. 3) (40). In patients with advanced duodenal disease (Spigelman stage III/IV, see below) (tab. 4), intensive surveillance and treatment may lead to reduc-
tion of duodenal cancer-related mortality [IV, B]. Surgical options include duodenotomy with polypectomy, pancreas-sparing duodenectomy and duodenal-pancreatectomy.

Because of the high recurrence rate of desmoid tumors, surgical resection should be delayed unless complications appear. The first line of treatment in patients with large or growing intra-abdominal or abdominal wall tumors is sulindac (300 mg), usually in combination with tamoxifen (40-120 mg), toremifene (180 mg) or raloxifene (120 mg) [III, C]. In patients with progressive intra-abdominal tumours that do not respond to this treatment, chemotherapy (e.g. doxorubicin and dacarbazine or methotrexate and vinblastine) or radiation therapy is indicated [III, B]. The role of surgery in intra-abdominal desmoids is controversial [III, B].

Tab. 4. Recommendations for management of duodenal polyposis in familial adenomatous polyposis, adjusted to the Spigelman stage of duodenal polyposis

<table>
<thead>
<tr>
<th>Spigelman stage</th>
<th>Endoscopic frequency</th>
<th>Chemoprevention</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>4 years</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Stage I</td>
<td>2-3 years</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Stage II</td>
<td>2-3 years +/-</td>
<td>+/-</td>
<td>No</td>
</tr>
<tr>
<td>Stage III</td>
<td>6-12 months +/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Stage IV</td>
<td>6-12 months +/-</td>
<td>+/-</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Surveillance

The risk of rectal adenoma and cancer remains after colectomy with IRA and even in the pouch after IPAA. Accordingly, regular endoscopic surveillance every 12 months after surgery is needed to detect adenoma recurrence early. Some patients with AFAP can be conservatively managed with annual colonoscopy and polypectomy [III, B].

Surveillance of duodenal adenomatosis will depend on its extension based on the Spigelman classification, since the risk of cancer appears to be related to stage. When it corresponds to Spigelman stage I upper endoscopy can be carried out every 5 years, whereas in stage II every 3 years. In more advanced forms intervals between examinations should be shortened to every 1 to 2 years (Spigelman stage III) or to 6 months (Spigelman IV) [III, B] (tab. 5).

Chemoprevention

Primary chemoprevention has never been demonstrated to delay the appearance of FAP.

Secondary chemoprevention with the use of non-steroidal anti-inflammatory drugs has been shown to reduce the number and extent of colorectal adenomas and, less reliably, duodenal adenomas. Accordingly, sulindac and celecoxib can be considered as adjuvant treatment when adenoma recurrence is detected after surgery. As cardiovascular side-effects have recently been reported in patients receiving selective COX-2 inhibitors, caution is warranted [II, B].

MUTYH-ASSOCIATED POLYPOSIS

Screening

Because of the similarity with AFAP, individuals should undergo total colonoscopy every 2 years, starting at the age of 18-20 years and continuing lifelong. Gene testing allows the most cost-effective screening to be carried out by driving colorectal examinations only to gene carriers. However, when the causative mutation is not identified, all at-risk family members should undergo colorectal screening [III, B].

Although less frequently than in FAP, patients with MAP may develop extracolonic manifestations, i.e. duodenal adenomas. Accordingly, upper endoscopy starting at the age of 25-30 years is recommended, following the same strategy described for APC-associated FAP [III, B].

Treatment

Colorectal management is similar to that proposed for patients with AFAP. Because of the small number of adenomas, in some patients endoscopic polypectomy can be considered. However, when polyp burden exceeds the number that could be safely managed by

Tab. 5. Surveillance recommendations

<table>
<thead>
<tr>
<th>Classic familial adenomatous polyposis</th>
<th>Attenuated familial adenomatous polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon and rectum</td>
<td>Colon and rectum</td>
</tr>
<tr>
<td>Sigmoidoscopy every 2 years, starting at age 12-14 years and continued lifelong in mutation carriers. Once adenomas are detected, annual colonoscopy should be carried out until colectomy is planned.</td>
<td>Colonoscopy every 2 years, starting at age 18-20 years and continued lifelong in mutation carriers. Once adenomas are detected, colonoscopy should be carried out annually.</td>
</tr>
<tr>
<td>Gastroduodenal adenomas</td>
<td>Gastroduodenal adenomas</td>
</tr>
<tr>
<td>Gastroduodenal endoscopy using both front and side-view scopes starting when colorectal polyposis is diagnosed or at age 25-30 years, whichever comes first. Surveillance intervals are based on the Spigelman stage.</td>
<td>Gastroduodenal endoscopy using both front and side-view scopes starting when colorectal polyposis is diagnosed or at age 25-30 years, whichever comes first. Surveillance intervals are based on the Spigelman stage.</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>Annual cervical ultrasonography, starting at age 25-30 years.</td>
<td>Annual cervical ultrasonography, starting at age 25-30 years.</td>
</tr>
<tr>
<td>Desmoid tumours</td>
<td>Desmoid tumours</td>
</tr>
<tr>
<td>Computed tomography (CT) scan or magnetic resonance imaging (MRI), if risk factors (positive family history for desmoids and site of the mutation in APC).</td>
<td>CT scan or MRI, if risk factors (positive family history for desmoids and site of the mutation in APC).</td>
</tr>
</tbody>
</table>
endoscopy, total colectomy with IRA should be offered. However, if rectal polypsis is severe, an IPAA is advised. Duodenal adenomas are usually managed as in AFAP [III, B].

Surveillance
After total colectomy, regular endoscopic surveillance of the rectum every 12 months is recommended. In patients conservatively managed with endoscopic polypectomy, colonoscopy should be carried out annually [III, B].

The suggested protocol for surveillance of duodenal adenomatosis in MAP patients is similar to that for AFAP [III, B].

Chemoprevention
So far, there is no evidence of the usefulness of any primary or secondary chemoprevention strategy in this setting.

REPRODUCTIVE OPTIONS
In some countries exist reproductive options for patients with mutation in the APC gene who does not wish to pass this alteration on to future children. However in Poland these procedures are forbidden.

1. Prenatal diagnosis. DNA is isolated from the cells of the developing baby through one of two procedures, chorionic villus sampling (CVS) or amniocentesis, and is analyzed for alterations in the APC gene. With appropriate counseling, a parent can then decide whether to carry the pregnancy to term or to end the pregnancy.

2. Preimplantation genetic diagnosis (PGD). For couples using in vitro fertilization to become pregnant, embryos can be tested for genetic disorders before transferring them into the uterus. Only healthy embryos carrying two working copies of the APC gene would be implanted. Before one can proceed with prenatal testing or PGD, an APC mutation must be identified in a parent with FAP.

CONCLUSIONS
Familial adenomatous polyposis is a serious condition which affects many people. Proper medical management and treatment of FAP is crucial to reduce morbidity.