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Surgical treatment of familial adenomatous polyposis in children: cross-sectional study

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ABSTRACT *Familial adenomatous polyposis (FAP) is an autosomal dominant disease caused by the APC gene mutation, characterized by colon adenomas and colorectal cancer, including in children. The issue of timing and indications for surgical treatment of FAP in childhood remains debatable.*

AIM: to identify predictors of surgery for FAP in pediatric patients.

PATIENTS AND METHODS: a retrospective case-control study included 50 children with FAP from January 2000 to April 2023 were analyzed. Two groups were formed: patients who underwent surgery of FAP under the age of 18 (case), and patients who did not undergo surgery at this age (control). We analyzed potential predictors: the age of manifestation, the clinical, the characteristics of adenomas, the anemia and family history, polyposis of the upper gastrointestinal tract.

RESULTS: in the surgical group, the proportion of patients with more than 100 adenomas was higher (23 (88%) versus 11 (45%) (p = 0.002)). It was revealed that the number of adenomas was more than 100 at the time of the first colonoscopy (OR 12 (95% CI (3–80), p = 0.02) and the presence of colon bleeding (OR 5.8 (95% CI 1–35, p = 0.03) are independent predictors of proctocolectomy in children.

CONCLUSION: the number of adenomas over 100 and colorectal bleeding are independent predictors of proctocolectomy in childhood.

KEYWORDS: *familial adenomatous poliposis, colproctectomy, children, ARS gene*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

Adenomatous polyposis syndrome (APS), familial adenomatous polyposis (FAP) is an autosomal dominant disease of the gastrointestinal tract characterized by the development of large intestine adenomas and colorectal cancer at the age, as a rule, older than 18 years in the absence of radical surgery [1,2]. APS is the second most common cause of colorectal cancer among hereditary polyposis syndromes [3]. The prevalence of the disease is 1–3 cases per 10,000, with the same lesion of both genders [4]. The disease is caused by various pathogenic variants of the *APC* (Adenomatous Polyposis Coli) gene — a tumor suppressor that suppresses the transmission of signals via the Wnt signaling pathway through the encoded protein [5,6]. A third of the pathogenic variants of the *APC* gene were found in its central region in the area between 1250 to 1464 codons and, according to some authors, causes a severe APS phenotype with early onset of the disease, early malignancy and a large number (hundreds and thousands) of adenomas in the large intestine [7,8]. Treatment of APS is reduced to the removal of the large intestine. At the same time, the question of the timing and indications for surgical treatment in childhood remains debatable. On the one hand, APS does not increase the risk of earlier development of colorectal cancer from adenoma, despite the fact that large intestine adenocarcinoma under the age of 18 is a relatively rare event [4,9,10]. Therefore, some specialists, including in our

country, are convinced of the need to find more reasoned indications for proctocolectomy in children and to perform surgery at an older age [11]. Others consider it necessary to perform surgery immediately after verifying the diagnosis of APS, since the malignancy of adenomatous polyps develops in 100% of cases, which means it is only a matter of time [12]. Ambiguities in surgical treatment of children with APS prompted us to analyze our own experience to identify predictors.

PATIENTS AND METHODS

An observational retrospective case-control study was done. It included 50 patients with APS who were on control at the Russian Children's Clinical Hospital from January 2000 to April 2023. The inclusion criteria were the age of the patient under 18 years, the presence of large intestine adenomas (according to the histological conclusion) and/or a confirmed pathogenic variant in the *APC* gene. The study did not include patients with other polyposis syndromes (juvenile polyposis syndrome, Peitz-Jaegers syndrome). Patient data (clinical and demographic characteristics of patients, photo and video materials of instrumental tests, protocols of pathomorphology) were obtained from case histories (paper, electronic) of the unit's archive. After receiving all the information, a data analysis was performed. The following factors were identified as potential predictors of surgical treatment for children with APS: gender, age at the time of the manifestation of the disease, family history of APS (presence of a parent with APS), clinical picture (intestinal bleeding), the presence of hereditary syndromes, as well as polyposis of the upper gastrointestinal tract (stomach and duodenum), as well as the same characteristics of adenomas (their number, size and degree of dysplasia at the time of the first colonoscopy (at the initial treatment of patients). The adenomas were counted *per haustra*. The size of the polyps was assessed by an endoscopist comparing the adenomas with 5 mm endoscopic biopsy forceps. Information on the degree of dysplasia (high and low degree) was obtained from the protocols of pathomorphology.

Statistical Methods

The data analysis was carried out using the GraphPad Prism statistical software package, version 9.3.1 (GraphPad Software, USA). The description of quantitative indicators was carried out with the indication of the median (25th; 75th percentiles), taking into account the incorrect distribution of variables. According to quantitative indicators, the groups were compared using the Mann–Whitney test, according to categorical ones — the χ^2 exact Fisher test. The differences between the groups were recognized as statistically significant at $p < 0.05$.Statistical relationships of potential predictors with the target outcome (surgery) were analyzed using univariate and multivariate logistic regression analyses. The multivariate analysis included indicators associated (at $p < 0.1$) with the target outcome based on the results of the univariate analysis. The relationship of potential predictors with the studied outcome was described with an indication of the odds ratio (OR) and 95% coincidence interval (CI). To test the diagnostic value of the multivariate regression model, the area under the curve (AUC), the likelihood ratio and the Hosmer-Lemeshov test were calculated.

RESULTS

The case histories of 50 patients with APS were analyzed. Two groups were formed from the number of patients who met the selection criteria: patients who underwent radical surgical treatment for APS (colectomy, proctocolectomy) under the age of 18 (case group), and patients who did not have surgery at this age (control group). Surgical treatment of APS was proctocolectomy with simultaneous J-pouch and the pouch-anal anastomosis, preventive ileostomy with subsequent closure of the ileostomy in 19 (73%) patients. Another type of procedure was colectomy with mucosectomy with ileorectal anastomosis in 7 (27%) patients. The median age at the time of surgery was 16 (14; 17) years.

Table 1. *Comparative characteristics of operated children and non-operated children with FAP*

Indicators	Children with FAP		*p*
	Operated (*n* = 26)	Non-operated (*n* = 24)	
Gender (female), abs. (%)	12 (46)	12 (50)	0.785
Age of APS debut, years	13.5 (8.5; 15)	14 (9.5; 14.5)	0.665
Age of the first colonoscopy, years	15 (11; 16)	14 (11; 15)	0.553
Family history of APS*, abs. (%)	21 (81)	19 (79)	0.887
Intestinal bleeding, abs. (%)	17 (65)	10 (41)	0.162
Maximum size of polyps**, mm	5.5 (4; 8.2)	5 (4; 8.5)	0.706
The number of polyps more than 100 **, abs. (%)	23 (88)	11 (46)	0.002
High degree of dysplasia**, abs. (%)	3 (11)	2 (8)	> 0.999
Stomach polyposis**, abs. (%)	8 (42)	6 (28)	0.509
Polyposis of duodenum**, abs. (%)	1 (5)	2 (9)	> 0.999
Presence of hereditary syndromes, abs (%)	3 (11)	4 (16)	0.697
History of polypectomy, abs (%)	6 (23)	10 (42)	0.128

*Note: APS — Adenomatous PolyposisSyndrome Duodenum; * The presence of a parent with APS; ** At the time of diagnosis of APS*

A comparative analysis revealed that operated and non-operated patients with APS were comparable in gender, age at the time of the onset of the disease, the presence of a family history of APS, hereditary syndromes, as well as the size and degree of polyp dysplasia. There was also no difference in the groups in concomitant polyposis of the upper gastrointestinal tract (stomach, duodenum) and in the number of endoscopic polypectomies performed in the history. In the group of operated patients, the proportion of patients with more than 100 adenomas was higher (23 (88%) versus 11 (45%) (p = 0.002)). Intestinal bleeding was more common in the group of operated patients in 17 (65%) patients than in the latter group — in 10 (41%) patients. However, statistical significance in the parameter could not be achieved (p = 0.1) (Table 1).

It was revealed by univariant analysis that the predictor 'the number of adenomas over 100' was significantly associated with surgery in childhood OR 9.06 (95% CI 2–33) (Table 2). Predictors with a value of $p < 0.1$, such as the number of adenomas over 100, the presence of intestinal bleeding and the presence of a history of polypectomies are included in the multivariate regression analysis. It was revealed that the probability of surgery in patients with more than 100 adenomas at the time of the first colonoscopy (OR 12.38 (95% CI (3–80), p = 0.02) and the presence of intestinal bleeding (OR 5.8 (95% CI 1–35, p = 0.03), are independent predictors of proctocolectomy in childhood (Table 2).

The diagnostic value of the regression model was determined. The area under the curve was 0.82 (95% CI 0.7–0.94), the predictive value of a positive result was 74%, the predictive value of a negative result was 83%, the likelihood ratio was 18.5 (p = 0.0004), the Hosmer-Lemeshov test was 5.1 (p = 0.5), which significantly confirms the predictive value of the obtained model.

Table 2. *Univariate and multivariate analyses of risk factors for surgery*

Indicators	Univariate analysis OR (95% CI), *p*	Multivariate analysis OR (95% CI), *p*
The number of adenomas at the first colonoscopy > 100	9 (2–33)	12.38 (3–80)
Intestinal bleeding	2.6 (0.8–7.7)	5.8 (1–35)
History of endoscopic polypectomy	0.39 (0.1–1.2)	0.2 (0.03–1.1)

DISCUSSION

The priority task in the treatment of patients with APS is the prevention of CRC, and, of course, maintaining a balance between the treatment and its radicality and the quality of life of patients.

Indications for surgery in APS in adults are suggested to consider an increase in the number of adenomas in follow-up, the size of adenomas > 6 mm in diameter, as well as the development of adenocarcinoma [13,14]. According to the ESPGAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) guidelines, surgery in APS in children should be performed in the presence of a large number of adenomas > 10 mm in diameter, or > 500 polyps > 2 mm in diameter, or with the so-called 'carpet covering' of the large intestine with adenomas. At the same time, it is clarified that these are weak recommendations with low quality of evidence. The guidelines also note the importance of deciding on the time of the surgery, taking into account social and personal factors, as well as the level of education [4]. Several studies were also conducted in order to find a correlation between the rate of progression of polyposis and the influence of this factor on surgical treatment of children with APS. However, no such correlation was found [15,16].

The approach of Russian surgeons for children with APS, as well as the factors on the basis of which a decision is made towards surgery remain uncertain and often subjective and may sometimes contradict existing recommendations.

With APS, there are situations when the severity of polyposis reaches a point at which endoscopic control of the large intestine is no longer accurate and safe to prevent CRC and relieve symptoms of the disease — the so-called 'uncontrolled polyposis'. These situations, regardless of the patient's age, require radical surgery. On the other hand, with a small polypous load of the large intestine, as well as compliance and a positive attitude of the patient to regular endoscopies, it is possible to perform colonoscopies with polypectomy of the largest or macroscopically altered adenomas, or with the removal of all existing adenomas with their minimal number and radical surgery at a later date. The results of our study have shown that the factor on the basis of which the decision was made on the need for surgery in children with APS was a large number of adenomas, namely the factor 'the number of polyps is more than 100'. It has also been demonstrated that factors such as a large number of large intestine adenomas and intestinal bleeding are independent predictors of proctocolectomy in childhood.

CONCLUSION

Indications for surgery for pediatric patients with APS remains actual among specialists dealing with this problem. The study demonstrated that the probability of surgery for a child with APS is higher with a large number of adenomas (more than 100) of the large intestine and the presence of intestinal bleeding.

AUTHORS CONTRIBUTION

Concept and design of the study: *Linara R. Khabibullina, Olga V. Shcherbakova*

Collection and processing of the material: *Linara R. Khabibullina*

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