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Juvenile polyposis syndrome (review)

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ABSTRACT *Juvenile polyposis syndrome (JPS), a rare disease with an autosomal dominant mode of inheritance, which is characterized with the presence of multiple polyps in various parts of the gastrointestinal tract, mainly in the colon. The detection of adenomatous polyps in patients with JPS, in addition to juvenile ones, significantly complicates the differential diagnosis with familial adenomatous polyposis, in which it is necessary to perform a radical surgery — proctocolectomy. Only in 40-60% of cases, pathogenic variants of the SMAD4 and BMPR1A genes can be identified, each of which is characterized with its own clinical manifestations. Treatment options for patients with JPS include endoscopic and surgical; however, the decision-making algorithm, as well as the timing of postoperative follow-up, are not evaluated in Russian clinical guidelines. The rare occurrence of this syndrome, difficulties in endoscopic diagnosis and morphological verification, as well as limitations in determining the molecular genetics cause of the disease demonstrate the need for further research.*

KEYWORDS: *juvenile polyposis syndrome, hamartomatous polyp, SMAD4, BMPR1A*

CONFLICT OF INTEREST: *authors declared no conflict of interest*

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INTRODUCTION

Juvenile polyposis syndrome (JPS) is an extremely rare disease (prevalence: 1:100,000 — 1:160,000) with an autosomal dominant type of inheritance characterized by the presence of multiple polyps in various parts of the gastrointestinal tract, mainly in the large intestine (98%) [1–4].

Only in 40–60% of cases, molecular genetic testsare able to identify pathogenic variants of the *SMAD4* and *BMPR1A* genes, each of which has its own clinical manifestations [5]. According to Jelsig, A.M. et al., in juvenile polyposis syndrome caused by a pathogenic variant of the *SMAD4* gene, lesion of the upper gastrointestinal tract is more common (in 70% of cases), and in the publication by Blatter, R. and co-authors, it is noted that the combination with hereditary hemorrhagic telangiectasia syndrome — Rendu-Osler-Weber disease in this group of patients is determined in 30% of cases [6,7].

In 70% of cases with large intestine lesions, juvenile polyps are localized in the rectum and distal part of the sigmoid colon, tend to bleed, self-amputation and prolapse [8]. The first clinical manifestations of the disease are nonspecific and most often occur before the age of 20. The difficulty in detecting this disease lies in the fact that in more than 50% of patients, in addition to juvenile polyps, adenomatous ones also occur, which makes it difficult to make a differential diagnosis with familial adenomatoses polyposis [9,10].

The analysis of literary sources revealed that the endoscopic characteristics of juvenile polyps are reflected only in a few publications [11,12].

Among all polypous syndromes in the development of colorectal cancer, the contribution of JPS is less than 1% [13]. At the same time, the risk of

colorectal cancer in this disease is up to 50%, and people with this syndrome are at increased risk of stomach and duodenal cancer — from 11% to 20% [14–16]. It is important to note that extra-intestinal cancers in patients with juvenile polyposis syndrome have not been described.

Given the rare occurrence of this disease, the issues of identifying diagnostic features, as well as studying the mechanisms of colorectal cancer development in this group of patients remain open. Recently, treatment options include endoscopic and surgical methods, but the decision-making algorithm, as well as the timing of postoperative follow-up, have not been developed yet.

Historical Aspects

The first description of juvenile polyps detected in the rectum of a 30-month-old child was performed in 1939 [17]. The term 'juvenile polyp' was first found in a publication by Horrilleno et al. in 1957 [18].

The authors described the results of examinations of fifty-five patients aged 1–14 years with juvenile polyps for the period of between 1935 and 1955. In 1966, Veale et al. identified distinctive macroscopic and histological features of juvenile polyps [19]. Initially, the disease was interpreted as characteristic of patients of the younger age group. Indeed, juvenile polyps occur in 2% of children and adolescents, accounting for 80–90% of the total number of polyps in this group of patients [20,21]. Sporadic (single) juvenile large intestine polyps occur in 2% of pediatric patients, as well as in patients over 18 years of age and are not associated with an increased risk of gastrointestinal cancer [22–24]. The term 'juvenile' defines the histological structure of the polyp, and not the age-related features of the disease [10].

Genetic Aspects of the Disease

To date, DNA diagnostics makes it possible to find the genetic cause of the disease in not all patients with juvenile polyposis syndrome. Pathogenic variants of the *SMAD4* or *BMPR1A* genes, which are located on chromosomes 18q21 and 10q22, respectively, can be detected only in 40–60% of cases in patients with JPS [5]. In about 20–30% of cases, JPS is caused by pathogenic variants of the *BMPR1A* gene, and in 20–30% by pathogenic variants of the *SMAD4* gene. Both genes are suppressors of tumor growth and are involved in the signaling pathways of bonemorphogenetic protein (BMP) and transforming growth factor beta (TGF-β), which affect cellular processes such as growth, differentiation and apoptosis [5]. Most variants are point mutations or small deletions/insertions in coding regions, and approximately 15% of variants are extended rearrangements [14,15]. Approximately 20–50% of cases of juvenile polyposis syndrome have no family history and are caused by *de novo* mutations [14–16,25].

According to one of the most comprehensive databases on mutations in the human genome, HGMD Professional, only 166 pathogenic variants in the *SMAD4* gene and 168 in the *BMPR1A* gene have been described in the world. It is likely that there are pathogenic variants of the genes associated with JPS that have notbeen identified yet.

Clinical Picture

The first clinical manifestations of the disease are more common in male patients (61%), occur before the age of 20 and include abdominal pain, diarrhea, blood secretion, as well as loss of polyps when they are localized in the rectum [3,8,44].

Based on the severity of clinical manifestations and the age of their occurrence, the following classification of juvenile polyposis was identified in 1975 [30]:

- Juvenile childhood polyposis, which is characterized by an earlier onset of symptoms and a more severe course of the disease;
- Juvenile large intestine polyposis and generalized juvenile polyposis are variable forms of the same disease, which are characterized by a later onset and a variety of clinical symptoms.

Juvenile childhood polyposis is a form that occurs in young children (the first manifestations are possible before the age of 1 year), which is characterized by the growth of polyps in the stomach, small

Table 1. *Differences in clinical manifestations depending on the pathogenic variant of the inherited gene*

Pathogenic Variant of *BMPR1A*	Pathogenic Variant of *SMAD4*
A rare lesion of the upper gastrointestinal tract	Lesion of the upper gastrointestinal tract in 70% of cases, high risk of stomach cancer
Adenomatous polyps are more common in the large intestine, mixed polyposis is characteristic, it is possible to detect colorectal cancer without the presence of polyps in the large intestine	Juvenile polyps are more common in the large intestine, it is possible to identify adenomatous ones
–	In 30% of cases, the combination with the syndrome of hereditary hemorrhagic telangiectasia

intestine and large intestine. Patients suffer from diarrhea, bleeding, and intussusception. According to the literature, in patients of the younger age group (from 5 to 14 years old) accumulation of polyps in 8% of cases leads to increased loss of serum proteins through the gastrointestinal tract with the development of severe hypoproteinemia (hypoalbuminemia, hypogammaglobulinemia) and edematous syndrome [26,29,30].

In severe cases of juvenile childhood polyposis, death usually occurs at an early age. In addition, many of these patients have congenital abnormalities, including macrocephaly and generalized hypotension [27]. Depending on the volume of lesion of the organs of the gastrointestinal tract, generalized juvenile polyposis and juvenile large intestine polyposis were separately highlighted [28]. To date, a unifying term has been adopted — juvenile polyposis syndrome. As a rule, the first clinical manifestations occur before the age of 20 years and depend on the pathogenic variant of the inherited gene [29,30].

Clinical Manifestations in Patients with Pathogenic Variant of the *SMAD4* Gene

Pathogenic variants of the *SMAD4* gene are associated with a more common lesion of the upper gastrointestinal tract (in 70% of cases) and an increased risk of developing stomach cancer (up to 20%) than in patients with the pathogenic variant *BMPR1A* [6,31–35]. In 30% of cases, a combination with hereditary hemorrhagic telangiectasia syndrome (HHT, Rendu-Osler-Weber syndrome) is possible [7,31]. The first manifestations in the form of nosebleeds in patients with HHT in 50–95% of cases occur before the age of 20. Hereditary hemorrhagic telangiectasia syndrome is exhibited in the presence of three or more of the following clinical criteria by Kurasao: spontaneous recurrent nosebleeds, multiple telangiectasia of the skin and mucous layers, the presence of vascular malformations in various organs, family history of the disease [36].

In the study by Lin, A.E. et al., it is noted that some pathogenic variants of the *SMAD4* gene lead to autosomal dominant Maira syndrome, a connective tissue disease with multisystem lesion and mental retardation [37].

Clinical Manifestations in Patients with Pathogenic Variant of the *BMPR1A* Gene

In carriers of the pathogenic variant of the *BMPR1A* gene, lesion of the upper gastrointestinal tract is rare, and manifestations of the disease in the large intestine range from the presence of mixed polyposis (both juvenile and adenomatous polyps are detected in the intestine) to the detection of colorectal cancer against the background of the absence of polyps in the large intestine [38]. Some authors even single out a separate type of polyposis syndrome — hereditary mixed polyposis syndrome (HMPS), noting at the same time its conditionality by pathogenic variants of the *BMPR1A* gene [39,40].

Based on the analysis of literature data, was compiled a table that reflects the various clinical manifestations of juvenile polyposis syndrome in those 40–60% of patients in whom the genetic cause of the disease was identified (Table 1).

To date, the clinical diagnosis of juvenile polyposis syndrome requires the presence of one of the following criteria [3]:

1) The presence of 5 or more juvenile polyps in the large intestine;

2) The presence of multiple juvenile polyps throughout the gastrointestinal tract;
3) Any number of juvenile polyps in the presence of this diagnosis in the family history.

Cancer Risk

Patients with juvenile polyposis syndrome are at increased risk of colorectal, small intestine and stomach cancer, but unlike patients with Peitz-Jaegers syndrome and adenomatous polyposis syndrome, extra-intestinal types of malignant neoplasms are not typical for this group of patients [41,42]. The cumulative risk of colorectal cancer ranges from 17% to 22% at the age of 35 and 68% at the age of 60 [4,43]. The mean age of diagnosis of colorectal cancer in patients with JPS is 34 years. Individuals with this syndrome are also at increased risk of developing stomach and duodenal cancer — from 11% to 20% [3,4,44,45].

Theories of Cancerogenesis

Previously, it was believed that malignant transformation of polyps in the case of JPS occurs as a result of permanent mechanical lesion and inflammatory changes [44,46].

In addition, there is a theory reflected in the sequence of hamartoma-adenoma-adenocarcinoma. As a result of the growth of polyps, dysplastic changes occur in them, which eventually leads to the development of adenocarcinoma [47]. In 1994, Subramony, C. et al. noted that neoplasms of less than 1 cm in size during pathomorphological examination have a structure characteristic of juvenile polyps. However, with an increase in size from 1 to 2.9 cm, the rate of dysplastic changes increases, with sizes larger than 3 cm, most juvenile polyps are covered with epithelium with dysplastic changes, visually looking like adenomas [48]. But considering that adenomatous neoplasms occur in more than 50% of cases in patients with juvenile polyposis syndrome, the most likely assumption is that colorectal cancer in patients develops from adenomatous structures, according to the classical path of cancerogenesis [49].

Endoscopic Picture

Polyps in juvenile polyposis syndrome are predominantly localized in the large intestine (98%), less often in the stomach (14%) and in the small intestine (7%) [3,44]. Their maximal number can reach several hundred. Juvenile polyps are hamartomas — they are formed from normal tissues of the intestinal wall in an unusual combination with a violation of the ratio of tissue elements and the predominance of stroma. The endoscopic picture of juvenile polyps is quite variable: juvenile polyps of the large intestine are localized in 70% of cases in the distal part of the sigmoid colon and in the rectum; they can be on wide bases with a size of several millimeters, as well as on legs with a size of several centimeters. Large polyps can be multilobed, whereas small polyps are usually round and smooth. Erosion and granulation tissue are often detected on the surface of polyps [11,50].

Infiltration of the mucosa surrounding polyps (a sign of 'chicken skin mucosa') is most often determined when polyps are localized in the sigmoid colon and rectum [51,52].

In the analysis of literary sources, an endoscopic description of the structure of juvenile large intestine polyps in JPS is found only in the studies by Brosens, L.A. et al., as well as in the ones by van Hattem, W.A. et al. [11,12].

In the publication by van Hattem, W.A. et al.,in total, the surface of 154 juvenile polyps was evaluated during endoscopic examination using stain and magnification, 20 of the polyps were also evaluated using endocytoscopy (using an ultra-high magnification endoscope — ×380). Endoscopic images were evaluated in terms of the general appearance of polyps, surface characteristics, color, pattern of epithelial pits and vascular architectonics [12].

According to the data obtained, the characteristic endoscopic signs of juvenile polyps are: hyperemia of the surface, the presence of erosion, caps of white mucus. When assessing the surface structure, open pits with inflammatory changes and a low density of the dimple pattern are revealed [12]. The open pits correspond to cystic-dilated glandular ducts filled with mucus. The low density

of the pits is due to the increased interstitial volume [53].

Despite the fact that juvenile polyps are considered benign, there are a few descriptions of juvenile polyps with dysplastic changes in the literature. O'Riordan et al. found that 7–14% of polyps in patients with JPS may have dysplastic changes [39]. In the study by Gao, X.H. et al. in a pathomorphological study of 767 neoplasms in patients with JPS, mild dysplasia was detected in 8.5% of polyps and severe dysplasia or adenocarcinoma in 0.3% of polyps [9].

According to the literature, a juvenile polyp without dysplastic changes more often has a smooth spherical, often eroded, surface. In the presence of dysplastic changes in the polyp, a lobed surface is more common and a villous component is present [12]. Given the rare occurrence of reports in the literature, additional studies are needed to confirm these conclusions. In addition to juvenile ones, these patients may also have adenomatous polyps, which makes it difficult to diagnose the disease [9].

Blatter, R. and co-authors conducted a retrospective cohort study, which included 221 patients with JPS from 10 European centers and found that adenomatous or dentate neoplasms in addition to juvenile polyps occur in 40–90% of cases [7].

In 2022, Rosner, G. and co-authors described 8 patients with genetically confirmed juvenile polyposis syndrome exclusively with adenomatous polyps in the large intestine [54]. It is important to note that it is impossible to describe the structure of juvenile polyps using the available endoscopic classifications [55–58]. In the article by Watanabe et al., it is noted that it is possible to detect gastric polyps in the absence of polyps in the large intestine [59]. As noted earlier, polyps of the upper gastrointestinal tract and gastric cancer are more often associated

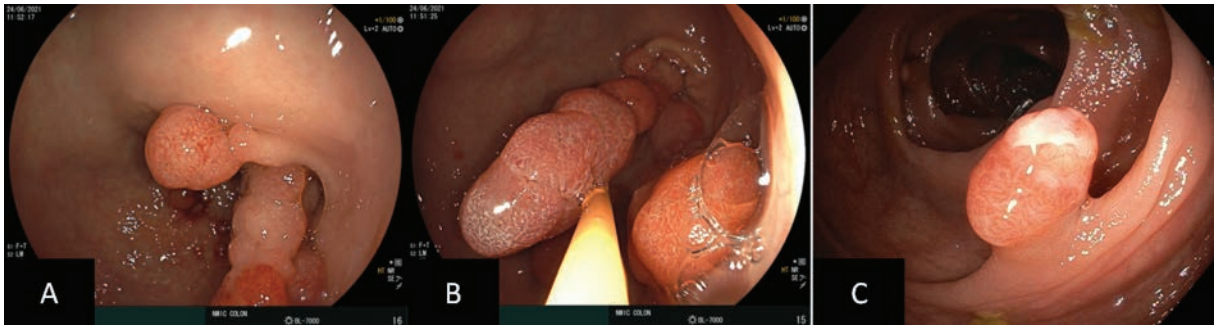

Figure 2. *Juvenile colon polyps (white-light examination) — from the archive of the Department of Endoscopic Diagnostics and Surgery of the Ryzhikh National Medical Research Center of Coloproctology*

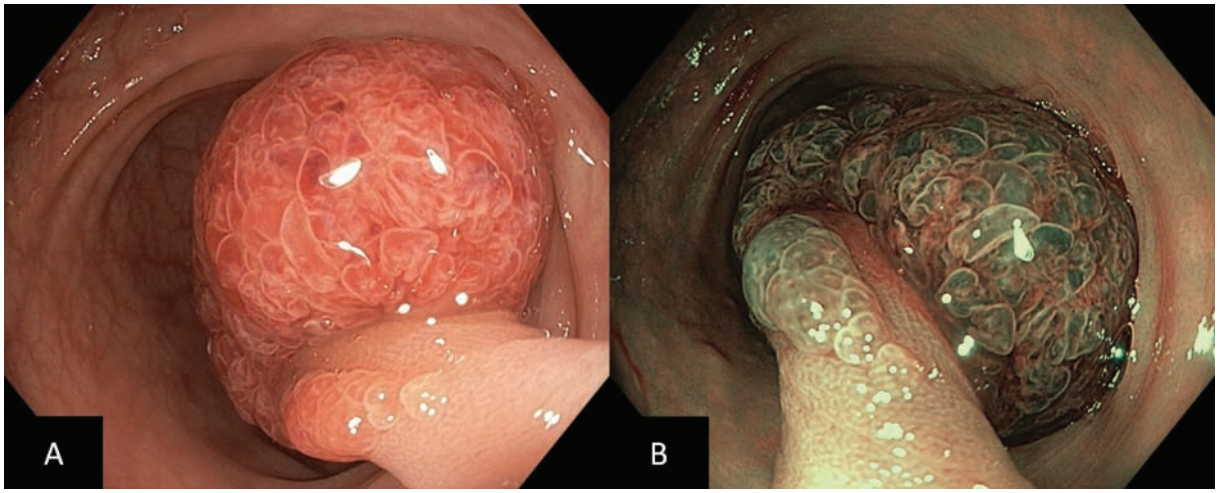

Figure 2. *Juvenile colon polyps (A. White-light examination, B. Narrow-band imaging examination) — from the archive of the Department of Endoscopic Diagnostics and Surgery of the Ryzhikh National Medical Research Center of Coloproctology*

with a pathogenic variant of the *SMAD4* gene [31–33]. Several studies focus on the lesion of the upper gastrointestinal tract in juvenile polyposis: polyps are predominantly hyperplastic and located in the antrum of the stomach [60–62]. It is also possible to identify such nonspecific signs as hyperemia, edema, contact bleeding of the mucous layer [6]. Leonard, N.B., Bronner, M.P. et al. described a clinical case of changes mimicking Menetrier's disease in a patient with genetically confirmed juvenile polyposis syndrome [63]. Polyps are rarely detected in the small intestine (in 7% of cases) and are mainly localized in the duodenum [3,44,64–66]. Wain et al. found that duodenal polyps are more common in carriers of the pathogenic variant of the *SMAD4* gene [65].

Morphology

Hyperplasia of mucinous glands and mucous cysts of different sizes are characteristic changes that are detected during the pathomorphological examination of juvenile polyps. These polyps consist of differentiated glandular ducts, and the glandular cavity is expanded to varying degrees.

This enlargement is usually accompanied by interstitial hyperplasia and infiltration of the stroma by a large number of inflammatory cells such as lymphocytes, plasma cells, neutrophils and eosinophils [67]. It is often difficult to distinguish juvenile polyps from inflammatory polyps at the morphological level [53,68].

Differential Diagnosis

To make a differential diagnosis, a thorough history collection, consideration of the clinical and endoscopic picture, the results of morphological examination and molecular genetic diagnosis are important. When carrying out a differential diagnosis of JPS, the following diseases and conditions must be taken into account: familial adenomatous polyposis syndrome (classical and attenuated form), *MutYH* -associated polyposis, Peitz-Jaegers syndrome, Cowden syndrome, inflammatory polyps and pseudopolyps of the large intestine (as a sign of previously pronounced inflammation), sporadic juvenile polyps, endometriosis of the large intestine (polypoid form) [80].

Treatment and Monitoring of Patients

Endoscopic removal of polyps is a priority treatment method for patients with juvenile polyposis syndrome [27]. According to the recommendations of the European Society for Gastrointestinal Endoscopy (ESGE), large intestine polyps larger than 1 cm should be removed [69]. The choice of endoscopic removal method depends on the endoscopic characteristics of the neoplasm and the equipment of the clinic. Currently, such techniques as polypectomy, mucosectomy (EMR), dissection in the submucosal layer (ESD) are available. Despite the priority of endoscopic treatment of this group of patients, its use is possible only with proper and timely diagnosis, which can be difficult, especially when endoscopic examination in the large intestine determines only adenomatous polyps, and molecular genetic examination fails to identify pathogenic variants of the *SMAD4* and *BMPR1A* genes. The literature describes cases when identified multiple polyps in the large intestine were treated as familial adenomatous polyposis syndrome and appropriate surgeries were performed [9,10].

The question arises what needs to be done first: a molecular genetic study, which does not always allow you to determine the diagnosis or directly begin surgical treatment?

Nowicki, M.J. et al., and Oncel, M. and co-authorsidentified the following criteria for performing surgical treatment: colectomy can be performed with a large number of polyps, large polyps or polyps with suspected malignant transformation [70]. Preventive radical surgery is indicated for patients with large intestine polyps that are not amenable to endoscopic treatment (> 50–100 polyps), juvenile polyps with dysplastic changes, as well as patients with severe gastrointestinal bleeding or diarrhea [71,72]. But given the active development of endoscopic surgery, these criteria may be revised.

Table 2. *Terms of endoscopic observation of patients with juvenile polyposis*

Age of the onset	Test
Since the age of 12–15	Colonoscopy every 1–3 years
Since the age of 18	EGDS in patients with a pathogenic variant of the *SMAD4* gene every 1–3 years, *BMPR1A* — the onset at 25 years old with an interval of 1–3 years

Surgical options include subtotal colectomy with ileorectal anastomosis or total proctocolectomy with pouch. As with *MutYH*-associated polyposis syndrome, the surgical scope of surgery may depend on the prevalence of polyps in the rectum [72]. If polyps are detected in the stomach, endoscopic treatment may be difficult, and patients with symptoms (for example, severe anemia) may require subtotal or total gastric resection [73]. After surgical treatment, patients need regular postoperative endoscopic follow-up, the timing of which is currently not clearly defined.

Screening and Follow-up

Currently, the national clinical guidelines do not contain an algorithm for the diagnosis, treatment and follow-up of patients with juvenile polyposis syndrome, which indicates the need for further research to develop and implement it [74,75].

Routine genetic testing of children at risk of JPS should begin at the age of 12–15 years. Children who develop rectal bleeding earlier than this age should undergo a colonoscopy, and then proceed to a genetic study to identify large intestine polyps [76].

Stool disorders (diarrhea), prolapse of polyps, blood excretion during the act of defecation, clinical manifestations of anemia, a positive stool test for occult blood are indications for endoscopic examination of the gastrointestinal tract. It is also necessary to perform an endoscopy in patients belonging to risk groups (for example, relatives of patients with polyposis syndromes) [77].

The timing of the start of endoscopy and follow-up are shown in Table 2. Colonoscopy is recommended for patients or relatives of patients starting from 12–15 years of age with an interval of once every 1–3 years. The timing of esophagogastroduodenoscopy depends on the identified pathogenic variant of the gene: in patients with a pathogenic variant of the *SMAD4* gene, every 1–3 years, starting at the age of 18.

In patients with a pathogenic variant of the *BMPR1A* gene, the onset is at the age of 25 with an interval of 1–3 years [69]. These follow-up periods are also reflected in the Japanese clinical guidelines of 2023 for the diagnosis and treatment of juvenile polyposis syndrome in children and adults [80].

Routine video capsule endoscopy is not recommended for this group of patients. Nevertheless, it can be used in patients with a pathogenic variant of the *SMAD4* gene and with the presence of vascular malformations (including presumably in the small intestine), with clinical manifestations of anemia, despite endoscopic removal of polyps and careful endoscopy [69]. ESGE experts recommend limiting the examination of the duodenum to patients with juvenile polyposis syndrome [78].

According to the recommendations of the HHT Foundation International, patients with the *SMAD4* mutation should be screened for vascular lesions associated with hereditary telangiectasia syndrome: at the time of diagnosis, they should be screened for the presence of vascular malformations of the brain, as well as undergo at least one MRI during puberty. Starting from the age of 35, patients need an annual assessment of hemoglobin or hematocrit levels [79].

If vascular malformation of the lung is detected at diagnosis, follow-up is recommended every 3–5 years with pulse oximetry and transthoracic echocardiography [79].

CONCLUSION

Given the extremely rare occurrence of juvenile polyposis syndrome, a variety of nonspecific clinical manifestations, the lack of well-developed endoscopic criteria, limitations in DNA diagnosis

Table 3. *Duration of observation of patients with hereditary telangiectasia syndrome*

Age of the onset	Study
Child's age (at the time of diagnosis)	Children need to be screened for the presence of vascular malformation of the brain and undergo at least 1 subsequent MRI during puberty
All patients over 35 years of age	Annual assessment of hemoglobin or hematocrit levels

of the disease, difficulties often arise in making a correct diagnosis. This literature review demonstrates the need for further research.

AUTHORS CONTRIBUTION

Concept and design of the study: *Tatyana A. Vlasko, Alexey A. Likutov, Alexey S. Tsukanov, Alexey A. Ponomarenko*
Collection and processing of the material: *Tatyana A. Vlasko*
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