ACTA FACULTATIS MEDICAE NAISSENSIS

UDC: 616.3-006:616-056.7

Scientific Journal of the Faculty of Medicine in Niš 2010;27(2):93-103

Review article ■

Hereditary Hamartomatous Gastrointestinal Polyposis Syndrome

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SUMMARY

Hamartomas represent localized overgrowth of cells in the parts which are normally associated with polyps, ie. mesenhimal, stromal, endodermal and ectodermal elements. Hamartomatous polyposis syndromes carry a significant risk of developing dysplasia, adenomas, gastrointestinal carcinomas, and pancreatic carcinomas. These syndromes may be classified on the basis of whether they represent hereditary syndromes or whether they occur on a sporadic basis. An overlap has been noticed among some of the syndromes. There have been described eight hereditary, and four non-hereditary hamartomatous poly pos syndromes. Hereditary syndromes include: Hereditary juvenile polyposis syndrome, Cowden syndrome, Bannayan-Ruvalcaba-Riley syndrome, Peutz-Jeghers syndrome, Nevus basal cell syndrome, Hereditary mixed polyposis syndrome, Neurofibromathosis type 1, and Multiple Endocrine Neoplasia type 2B. All of these syndromes are inherited in an autosomal dominant fashion. Non-hereditary syndromes include: Cronkhite-Canada syndrome, hyperplastic polyps, lymphoid polyposis, lymphomatous polyposis. The diagnosis of these syndromes primarily remains a clinical process. Treatment of these patients requires a coordinated multidisciplinary approach which includes gastroenterology, pathology, dermatology, surgery, oncology, and genetics.

Key words: **hamartomatous polyps, juvenile polyps, Peutz-Jeghers syndrome, Cowden syndrome, genetics**

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INTRODUCTION

Polyps of gastrointestinal (GI) tract could be sporadic or included in polyposis syndromes. The term polyp comes from the greek word «polypus», meaning «many footed». It is used to name pedunculated growths of intestinal mucosa.

The most frequent polyps of gastrointestinal tract are adenomes, while hamartomatous polyps are rarely present. Hamartomas are tissue masses composed of locally proliferated cells with irregular organisation, with mesenchymal, endodermal and ectodermal parts. Hamartomatous polyposis syndromes bring significant risks for further development of dysplasia, adenomas, gastrointestinal cancers, and pancreatic cancers (1).

Hamartomatous polypous syndromes are classified into hereditary and nonhereditary, however with overlapping between some syndromes. Nine hereditary and four nonhereditary hamartomatous polyposis syndromes have been recognised. Hereditary syndromes have autosomal - dominant types of hamartomatous polypes. Nonhereditary syndromes are: Cronkhite - Canada syndrome, hyperplastic polyps, lymphoid polyposis, and limphomatous polyposis.

Famlilial juvenile polyposis syndrome, and Peutz - Jeghers syndrome are the most frequent (2, 3).

For the diagnosis of specific polyposis syndrome, it is necessary to have information about: a) number of polyps and their localisation, b) patient`s age, 3) family history, d) other clinical information about patients having specific syndromes.

CLASSIFICATION OF HEREDITARY HAMARTOMATOUS POLYPOSIS SYNDROMES

Classification of hereditary hamartomatous polyposis syndromes is given in Table 1.

Table 1. *Classification of hereditary hamartomatous polyposis*

Hereditary syndromes
Hereditary juvenile polyposis syndrome
Cowden Syndrome
Bannayan-Ruvalcaba-Riley Syndrome
Peutz-Jeghers Syndrome
Basal Cell Nevus Syndrome
Hereditary Mixed Polyposis Syndrome
Neurofibromatosis Type 1
Multiple Endocrine Neoplasia Type 2B (MEN2B)

HEREDITARY JUVENILE POLYPOSIS SYNDROME

Hereditary juvenile polyposis syndrome (JPS) is a rare disorder, the incidence of which is aproximately one case per 100. 000. JPS is the most frequent among hamartomatous syndromes, and it is characterized by multiple, hamartomatous polyps of colon and rectum. Unlike sporadic juvenile polyps (the most frequent form of polyp in pediatric population - with the incidence of 2%), JPS are more numerous, and could be localized in the proximal parts od gastrointestinal tract (3). This polyps have smooth, and transparent appearance.

On histopathology examination, the polyps are composed of significantly enlarged glands containing mucus, with edema and inflammatory lympho-plasmocytic infiltrate in lamina propria. Proliferation of smooth muscle cells is absent, and muscular layer of mucosa is partially attenuated by inflammation (3).

The JPS is associated by enhanced risk for development of colonic, gastric, intestinal, and pancreatic carcinoma. This cancer arises from adenomatous components of juvenile polyps (4). The incidence of colon cancer is 17-22% by the age of 35, and approximate 68% by the age of 60. The presence of invasive colorectal cancer indicates surgical treatment with or without ileocecal anastomosis depending of rectal involvement. Current guidelines for the following JPS are given in Table 2.

JPS could be diagnosed if any of the following three criteria is present:

- multiple (3-10) hamartomatous polyps of colon;
- any number of hamartomatous polyps in patients with family history of JPS;
- extracolonal hamartomatous polyps.

Clinically, JPS is often obscure. Obstruction and gastrointestinal bleeding could be the signs of JPS (12). JPS could coappear with hereditary hemorrhagic teleangiectasias (Osler-Weber-Rendu syndrome), which bears the risk for aneurism development or pulmonary thrombosis (5).

JPS follows autosomal - dominant scheme of inheritance. Currently, two genes are known, 1) MADH4 (*Mothers Against Decapentaplegic Homolog 4*, which is sometimes named SMAD4, and 2) BMPR1A (*Bone Morphogenetic Proteinic Receptor type 1A*).

MADH4 is located at chromosome 18q21.1, and it is found in 15% of patients with JPS. MADH4 have proteinic code associated with cellular responses (growth, apoptosis, growth disturbances) mediated throught transformed beta growth factor (TGF-β).

BMPR1A, located at 10q22.3, is a member of TGF-β family. It codes its serin-treonin kinasis, which is involved together with MADH4 in bone morphogenetic signaling. It is identified in approximately 25% of famlily cases (6).

Aproximately, 25% of newly discovered patients with JPS have sporadic new mutations, of which 75% bring family history (6).

Table 2. *Guidelines for JPS screening*

Testing on cancer	Age at which examinations should begin *	Intervals	Diagnostic tests
Colon	15	Each second year +	Colonoscopy
Proximal GI tract	15	Each second year +	Upper endoscopy
Small intestine			UGI w/SBFT
Breast §	21	Monthly Per 6-12 months	Clinical examination
Thyroid gland ξ	Adolescence	Once a year	Clinical examination *+ basic U/S

* early if symptomatic

\+ once a year if polyps are diagnosed

§ intervals for examination could be extended after the age of 35 in risk patients: gene inheritance and diseased should follow with similar dynamics

ξ especially if mutation of PTEN is discovered: yearly mammography begins at the age of 30 or later; UGI w/SBFT (upper gastrointestinal with/small bowel follow-through)

COWDEN SYNDROME

Cowden syndrome (CS), or multiple hamartomatous syndrome is a disease which should be differentiated from JPS. CS is less frequent than JPS, with the prevalence of 1 per 200. 000 cases. CS, as well as JPS is inheritated in an autosomal dominant fashion. It is characterized with multiple hamartomatous tumours of ectodermal, mesodermal, and endodermal origin. Its manifestations are most obvious on the skin, intestine, mammary glands, and thyroid (7). Occasionally, hamartomatous polyps of gastrointestinal tract could not be differented from JPS polyps. Also, ganglioneuromas, lipomas, and inflammatory polyps could be developed in gastrointestinal tract. Patients with Cowden syndrome could develop glycogene acantosis of oesophagus as well.

Contrary to JPS, patients with Cowden syndrome develop numerous extraintestinal clinical manifestations (Table 3).

The most striking are mucocutaneous lesions: facial trichilemmomas, acral acantosis, subcutaneous lipomas, palmo-plantar keratoses, oral cobblestoning and oral papillomas. Moreover, dermatological manifestations of the syndrome are present in 80% of the patients (7).

Progressive macrocephaly, highly arched palate, hipoplastic mandible and maxilla, and microstomias could be developed on the head and neck. On breasts, supernumerary nipples and pectus excavatum could be seen. Hemangiomas, neurinomas, cysts of ovaries, as well as uterine leiomyomas could be found (8).

Benign mucocutaneous manifestations of Cowden syndrome allmost allways develop in early childhood, before the appearance of neoplastic lesions. Recognising of this benign signs of the disease has essential significance for early establishing of diagnosis and initiating adequate clinical examinations, and tests on cancers.

Patients with Cowden syndrome greatly increase the risks for development of breast and thyroid gland cancers. Benign lesions of this glands, such as nontoxic multinodal thyroid struma, thyroglossal ductal cysts, and fibrocystic disease of breast, could be also present. Breast cancer is the most serious complication of Cowden syndrome, and it could be found in 36% of patients (7). Risk for thyroid carcinoma development is 10%, and the risk for cancer development in other organs, ovaries, cervical, uterine, urinary bladder, and meningeomas, is also present (8).

Table 3. *Extraintestinal manifestations of hereditary hamartomatous gastrointestinal polyposis sindromes*

JPS	Other	Pulmonary arteriovenous malformations Digital clubbing
Cowden Syndrome	Dermatological	Papillomatous papules Acral/plantar keratoses, Trichilemmomas
	Endocrinological	Malignant tumors of thyroid gland
	Gonadal	Endometrial cancers Benign fibromas
	Head and neck	Brain tumors Macrocephaly Dolichocephaly
	Others	Breast cancers Renal cell carcinoma
Bannayan-Ruvalcaba-Riley Syndrome	Dermatological	Lipomas Pigmented macules of glans penis
	Head and neck	Macrocephaly
	Musculosceletal	Myopathy of proximal muscles Hypersensitivity of joints Pectus excavatum Scoliosis
	Neurological	Developmental delay Mental disorders
	Others	Overweight newborn
Peutz - Jeghers Syndrome	Dermatological	Hyperpigmentation • Dark blue to dark brown macules around mouth, eyes, nostrils, perianal region, and buccal mucosa. • Hyperpigmented maculas on fingers
	Endocrinological	Thyroid cancer
	Gonadal	SCTAT Tumors of Sertoli`s cells of testis Gynecomastia Malignant tumors of cervix Ovarial cancers Ovarial cysts
	Pulmonary	Bronchial polyps Lung cancer
	Urological	Urethral polyps Urinary bladder polyps
	Other	Pancreatic cancer Breast cancer

Syndrome of Basal Cell Nevus	Dermatological	Harsh facial features
		Renal cell cancer
	Head and neck	Keratocysts of jaws
		Macrocephaly
		Prominent forehead
		Facial milia
		Medulloblastoma
	Other	Fibromas of heart and ovaries
Neurofibromatosis tip 1	Dermatological	Cafe au lait spots
		Neurofibromas of skin
		Additional speckles
	Head and neck	Hamartomas of iris, Lish nodules
		Optic gliomas
		Other central nervous neoplasms (i.e. astrocytomas)
		Brain gliomas
	Musculosceletal	Pseudoarthrosis
		Bone dysplasia
		Scoliosis
		Low body height
	Neurological	Cognitive disabilities and learning problems
		Seizures
		Macrocephaly
	Oncological	Chronic myeloid leukemia in children
		Neurofibrosarcoma
		Pheochromocytoma
Multiple Endocrine Neoplasia Syndrome Type 2B	Head and neck	Ganglioneuroma of lip mucosis and tongue
		Elongated face with prominent lips
	Endocrine	Medullary thyroid carcinoma
		Pheochromocytoma
	Others	Marfanoid body habitus

While high breast and thyroid cancer risks are well documented, there is no clear relation between Cowden syndrome and gastrointestinal cancers, as was previously beleived. Guidelines for the diagnosis of Cowden syndrome is systematized in Tables 4 and 5 (9).

Approximately 80% of CS patients develop primary mutation of PTEN tumour - supressor gene, located at chromosome 10q23. PTEN inhibits growth, checking cell proliferation, which is potentiated by tirosine kinase. So far, no other gene mutations have been discovered. Whereas the disease is not fully understood, it could not be argued about relationship between sporadic and familial cases.

Table 4. *Surveillance recommendations for Cowden syndrome*

Cancer screening	When to start[1] (age)	Intervals[2]	Diagnostic tests[3]
Colon	15	Per 2 years	Colonoscopy
Proximal GI tract/small intestine	15	Per 2 years	Upper endoscopy
Breast	21	Monthly	Selfexamination
Breast	30	Once a year	Mammography
Thyroid gland	Puberty	Once a year	Clinical examination

[1] - even earlier if symptomatic

[2] - once a year if polyps are diagnosed

[3] - intervals between examinations could be extended in risk patients older than 35; gene inheritance and disease should follow with similar dynamics.

[4] - definite consensus has not been established

Table 5. *Diagnostic criteria for Cowden syndrome - International Cowden Syndrome Consortium, version 2000*

Pathognomonic criteria	Major criteria	Minor criteria
Facial trichilemmomas	Breast cancer	Other thiroid lesions Mental retardation Hamartomatous intestinal polyps
Acral keratosis	Thyroid carcinoma (especially follicular type)	
Papillomatous papules	Macrocephaly	Fibrocystic breast disease
Lesions of mucosa	Lhermitte-Duclos* disease Endometrial cancers	Lipomas Fibromas GI tumors GI malformations

* Lhermitte - Duclos disease (LDD) is defined based on dysplastic cerebral gangliocytomas presence

BANNAYAN-RUVALCABA-RILEY SYNDROME

The Bannayan-Ruvalcaba-Riley Syndrome (BRRS) comprises three disorders: Bannayan-Zonana syndrome, Riley-Smith syndrome and Ruvalcaba-Myhre-Smith syndrome.

Intestinal polyposis is present in 45 % of these patients. Usually, multiple hamartomatous polyps are present in the distal part of ileum and colon, althought they can be seen along gastrointestinal tract. Histopathologically, they are similar to polyps of JPS.

Germline mutations of PTEN gene are found in BRRS. Marsh et al. indicate that 60 % of patients with BRRS have PTEN gene mutation (10). This poses a question if CS and BRRS are allelic, and wheather they are one syndrome with wider spectrum. Families with overlapping between CS and BRRS syndromes have PTEN gene mutation. Marsh et al also noted the presence of PTEN mutation associated with lipoma and breast tumours onset. Few BRRS patients do not have PTEN mutation. Therefore, different mutations or deletions in various parts of PTEN gene could be responsible for the onset of BRRS, contrary to CS.

The risk for development of cancers in patients without PTEN mutation has not been clearly explained yet (10). Genetics of hereditary hamartomatous polyposis syndromes are given in Table 6.

Table 6. *Genetics of Hamartomatous Polyposis Syndromes*

Syndrome/OMIM classification	Gene location	Product
JPS 174900	MADH4(SMAD4) 18q21.1 BMPR1A 10q22.3	*Mothers against decapentaplegic homolog 4* Bone morphogenetic proteinic receptor 1A
Cowden syndrome 158350	PTEN 10q23.31	Phosphatase of dual specificity PTEN
BRR syndrome 153480	PTEN 10q23.31	Phosphatase of dual specificity PTEN
Peutz-Jeghers syndrome 175200	STK11(LKB1) 19p13.3	Serin/treonin-protein kinase 11
Syndrome/OMIM classification	Gene location	Product
Basal cell nevus syndrome	PTCH 9q22.3	Pathched protein homolog 1
Hereditary mixed polypous syndrome 601228	HMPS/CRAC1 15q13q-q14	/
Neurofibromatosis type 1	NF1 17q11	Neurofibromin
Multiple Endocrine Neoplasia Syndrome type 2B 162300	RET 10q11.2	RET tirosin-protein kinase receptor

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is an autosomal-dominant hamartomatous polypous syndrome associated with mucocutaneous hyperpigmentation. Its prevalence is 1 per 200 000 cases. The disease is variously manifested, even within one family: some family members have only hyperpigmentation, while others have hyperpigmentation and intestinal polyps (11). Contrary to JPS, where polyps arise in the colon, hamartomatous polyps of PJS are usually present in the small intestine, as well as in the stomach, and large intestine. Average time for the onset of first polyps is at the age of 11, however with broad time range, with exception for polyposis developed at birth. These polyps typically arise in early adolescence (11). Clinical gastrointestinal manifestations of the disease include intussusception and intestinal obstruction, which requires repeted laparotomies and gut resections, as well as chronic bleeding and anemia.

Extraintestinal signs, usually precede gastrointestinal manifestations, and develop from birth to childhood, including mucocutaneous hyperpigmentation (dark blue to dark brown maculas around mouth, eyes, nostrils, perianal region, and on buccal mucosa). Hyperpigmented maculae on fingers are frequent. Pigmented lesions could fade during puberty and adulthood. Extraintestinal polyps can also appear. Hamartomatous polyps of urinary bladder, pelvicis, and lungs have been reported.

Female patients bear the risk for the development of sex cord tumours with annular tubules (SCTAT), benign neoplasms of ovaries, as well as malignant tumours of cervix. Male patients sometimes develop testicular tumours of Sertoli`s cells, which could produce estrogenes, causing gynaecomastia. PJS have high risk of intestinal and extraintestinal malignancy onset, including colorectal cancers, cancers of oesophagus, gastric cancers, cancers of small intestine, breasts, ovaries, and pancreas (1).

Diagnosis of PJS is based on clinical findings and histopathological patterns of polyps. The polyps present unique morphology, composed of mucosis with interdigiting smooth muscle bundles, which have characteristic appearance of a tree and its branches, named «arborisation». PJS polyps could move epithelial structu-

res deeper into muscularis propria which have the appearance of pseudocarcinomatous invasion.
Hamartomatous-adenomatous-cancerous evolution was evidenced in stomach, small intestine, and colorectal polyps of PJS. Larger hamartomatous lesions usually contains focuses of adenomatous change.

Parameters for definite diagnosis of PJS according to histopathologically confirmed the presence of hamartomatous polyps, and at least two of the following clinical criteria: 1) family history, 2) hyperpigmentation, and 3) polyposis of small intestine. The most certain diagnosis is based on two of three criteria, without histopathologic verification of hamartomatous polyps.
Afterwards, genetic testing is recomended for the confirmation of diagnosis.

In cases of PJS where relatives of first order have PJS, the presence of mucocutaneous hyperpigmentation is sufficient for the making this diagnosis.

Until now, the only identified mutation which is associated with PJS has been on STK11 gene (serin/-treonin protein kinase 11, which is also known as LKB 1), located at the chromosome 19p13.3. STK11 codes multifunctional serin-treonine kinase which is involved in intercellular transfer of growth signals; it functions as the gene for tumour supression. PJS is inherited in an autosomal dominant fashion. However, up to 25% of recorded cases do not have family history. Those sporadic cases probably arise due to new mutation of STK11 gene or low penetration.

Risk patients, however not diseased patients, which do not fulfill criteria, are considered close relatives of PJS patients. During chilhood, invasive examination is contraversial, except in cases of symptoms presence. Guidelines for cancer screening are given in Table 7.

Table 7. *Recommendations for examinations for PJS*

Cancer	When to start with screening (age)	Intervals	Diagnostic tests
Colon	25	Once per 2 years	Colonoscopy
Proximal GI tract /small intestine	10	Once per 2 years	Upper endoscopy
Pancreas	30	Once a year to once in two years	Endoscopic ultrasound Transabdominal ultrasound
Breast	20	Once a year	Mamography Self - examination
Uterus	20	Once a year	Transvaginal ultrasound Endometrial biopsy PAPA test
Cervix	20	Once a year	Physical examination
Testes	10	Once a year	Ultrasound - if clinical indications are present

BASAL CELL NEVUS SYNDROME

Basal cell nevus syndrome (BCNS), also known as Gorlin-Goltz syndrome is a rare disease which is inherited as an autosomal-dominant trait, by mutation on PTCH gene. It is characterized by multiple basal cell carcinoma (BCCs), other tumours such as medulobllastoma, as well as developmental anomalies including macrocephaly, spina bifida, palmar and plantar pits, and bone cysts especially of mandible. Multiple basal cell carcinoma are the most frequent in this syndrome; this diagnosis should be taken into consideration when few such lesions are present before the age of 35 (12). Persons with fair skin have significantly higher risk for development of multiple basal cell carcinomas.

Hereditary mutations in BCNS patients, and somatic mutations in sporadic cases are identified at human homologue of Drosophilla gene (PTHC gene).
PTCH gene codes intramembranous protein is responsible for cell displacement and growth in various tissues. The gene is located at chromosome 9q22.3. Approximately 20 to 30% of BCNS cases develop with new mutations of PTCH gene, and do not have any previous family history of the disease.

The presence of polyps is not the major characteristic of the syndrome. Most of the families with this disorder do not have gastrointestinal manifestations.

Considering that this syndrome is exceedingly rare, screening on gastrointestinal neoplasms are not necessary.

HEREDITARY MIXED POLYPOSIS SYNDROME

Hereditary mixed polyposis syndrome (HMPS) is considered as a variant of JPS which is characterized by hamartomatous polyps and adenomas. HMPS presents in various colorectal tumours, including atypical juvenile polyps, hyperplastic polyps with focuses of dysplasia (serrated adenomas), classical adenomas, and carcinoma. Only one case of this syndrome has been described in one family, St. Mark family 96 (SM96). In this family it was found that young members had atypical juvenile polyps and/or hyperplastic polyps, while older relatives had cancers. This research indicate that natural history of the disease is advancing from hyperplastic polyps to serrated adenomas and carcinoma. It apears that this disease targets only colon, and without reported other gastrointestinal or extraintestinal manifestations (13). Newer genetic research points out that the disease is located at 15q13-q14. Beside this, the part which contains HMPS gene overlaps with the part which bears CRAC1 (gene for colorectal adenoma and carcinoma). CRAC1 is newly discovered gene associated with carcinoma development and located at 15q14-q22. Currently, those two genes are considered identical.

NEUROFIBROMATOSIS TYPE 1

Although, neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, is usually not considered as hamartomatous polyposis syndrome.
Multiple submucous neurofibromas, which cause dyspepsia, abdominal pain, and gastrointestinal bleeding can also develop in the same patient. If gastrointestinal tract is involved, it is only sporadic and asymptomatic. This disease is usually characterized by numerous «cafe au lait» spots on skin, inguinal maculas, multiple skin neurofibromas, and pigmented lesions of iris Lish nodule (14).

Along with described syndromes, NF1 also has autosomal-dominant inheritance. In nearly half of the patients with NF1, a new sporadic gene mutation is responsible for the onset of the disease. Although the disease is based on mutations of NF1 gene (which is located at 17q11), even genetic analyses are available, diagnosis could be established solely on specific clinical signs. Normal gene product is neurofibromin, which function has not been clearly defined jet. It seems that it activates GTP-asis and regulates ras-gene, controling cell proliferation, and works as antioncogene.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B

Multiple Endocrine Neoplasia type 2B (MEN 2B) is one of three subtypes of Multiple Endocrine Neoplasias type 2 Syndrome (MEN 2); other two subtypes of this disease are MEN 2A, and familial medullary thyroid carcinoma. The prevalence of MEN 2 is 1 per 300.000 cases, and five percent of that is reserved for MEN 2B. Abdominal distension, with numerous polyps, megacolon, constipation, and diarrhoea could be the manifestations of polyposis. Other clinical characteristics of MEN 2B includes mucosal neuromas of lips and tongue, typical face with enlarged lips, asthenic and marfanoid body habitus, as well as prominent, corneal nerves thickening. Two the most threatening complications of the syndrome are:
1) high risk for medullary carcinoma development in early years of life and,
2) higher risk for the onset of pheochromocytoma, which is documented in 50% of MEN 2B cases. Patients who do not undergo through thyroidectomy early in life have the chance to develop metastases of medullary thyroid carcinoma, where average life expectancy is estimated to 21 years. Unlike MEN 2A, patients with MEN 2B usually do not have abnormalities of parathyroid gland (15).

MEN 2B is inherited as an autosomal - dominant trait. Mutations in RET gene (chromosome location 10q 11) are identified in 95% patients with MEN 2B. Most of the patients with MEN 2B phenotype have mutation only on one part of tirosine kinase RET gene at codon 918 in exon 16, which changes treonine with metionine. Up to 50% of cases are caused by spontaneous mutation in this gene without previous family history of the disease.

CONCLUSION

Hereditary hamartomatous gastrointestinal polyposis sindromes are inherited in autosomal dominant fashion. Significant number of patients do not have family history, and develop new gene mutations. Many of the syndromes heighten significantly the risk for gastrointestinal cancer development.

Diagnosis of the hereditary hamartomatous gastrointestinal polyposis sindromes is primarily based on clinical examination. Endoscopic results, extraintestinal (especially dermatological manifestations), and family history should alert physician on specific hamartomatous syndrom. Identification of major target genes induced reclassification of the syndromes.

Therapy of patients with hereditary hamartomatous gastrointestinal polyposis sindromes demands multidisciplinary approach, which comprises gastroenterology, pathology, dermatology, surgery, oncology, and genetics.

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NASLEDNI HAMARTOMATOZNI GASTROINTESTINALNI POLIPOZNI SINDROMI

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Sažetak

Hamartomi su lokalizovano umnožavanje ćelija u delovima gde se polipi obično javljaju, tj. mezenhimalnih, stromalnih, endodermalnih i ektodermalnih elemenata. Hamartomatozni polipozni sindromi nose značajan rizik za razvoj displazije, adenoma, gastrointestinalnih karcinoma i karcinoma pankreasa. Ovi sindromi mogu da se klasifikuju na hereditarne i nehereditarne. Postoji preklapanje između pojedinih sindroma. Opisano je 8 hereditarnih i 4 nehereditarna hamartomatozna polipozna sindroma. Hereditarni su: Hereditarni juvenilni polipozni sindrom, Cowden-ov sindrom, Bannayan-Ruvalcaba-Riley sindrom, Peutz-Jeghers sindrom, Sindrom bazalnih ćelija nevusa, Nasledni mešoviti polipozni sindrom, Neurofibromatoza

tip 1 i Multipna Endokrina Neoplazma tip 2B. Svi ovi sindromi se nasleđuju autozomno-dominantanim načinom.
U nehereditarne sindrome spadaju: Cronkhite-Canada sindrom, hiperplastični polipi, limfoidna polipoza, limfomatozna polipoza. Dijagnoza ovih sindroma ostaje primarno klinički proces. Lečenje ovih bolesnika zahteva koordinisani multidisciplinarni pristup koji obuhvata gastroenterologiju, patologiju, dermatologiju, hirurgiju, onkologiju i genetiku.

Ključne reči: **hamartomatozni polipi, juvenilni polipi, Peutz-Jeghers sindrom, Cowden sindrom, genetika**