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Selected syndromes of hamartomatous polyposis of the gastrointestinal tract – clinical and genetic aspects

Tomasz Pytrus[1], Karolina Pesz[2], Anna Kofla-Dłubacz[1], Andrzej Stawarski[1], Justyna Gil[2]

[1] *2nd Department of Paediatrics, Gastroenterology and Nutrition, Faculty of Medicine, Wroclaw Medical University, Wroclaw, Poland*
[2] *Department of Genetics, Faculty of Medicine, Wroclaw Medical University, Wroclaw, Poland*

Hamartomatous polyp syndromes are a clinically and genetically heterogenous group of rare disorders that fall into the category of inherited predisposition to cancer. They include Peutz-Jeghers syndrome, Cowden syndrome, juvenile polyposis and mixed hereditary polyposis. Although the shared common characteristic is the presence of multiple polyps in the gastrointestinal tract, they differ by the number, age of onset and histopathological features of the polyps, clinical picture and presentation, as well as the approach to genetic testing. With the recognition of the importance of providing high quality medical care, that is equal diagnostic and therapeutic opportunities to patients with rare disorders (Uchwała nr 110 Rady Ministrów z dnia 24 sierpnia 2021 r. w sprawie przyjęcia dokumentu „Plan dla chorób rzadkich"), the authors would like to present the essential (fundamental) aspects of the above-mentioned syndromes.

Key words: hamartomatous polyps, clinical presentation, genetics

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) was originally described by J.L.A Peutz in 1921 as a co-occurrence of gastrointestinal polyposis and pigmentations in a single family. Then later, in 1949, H. Jeghers published a summary of the signs and symptoms of the disorder, based on the clinical picture of unrelated patients [1].

Peutz-Jeghers syndrome is inherited in an autosomal dominant manner, however up to 40% of mutations occur *de novo* (hence there is no family history of the disorder). PJS is caused by a heterozygous pathogenic variant in the *STK11* (serine/threonine kinase 11) gene and so far, this is the only gene that has been connected to the disorder. Most of the described mutations are point mutations that can be found on sequencing but a quarter of the pathogenic variants are so-called large gene rearrangements (duplication/deletion of exon/exons). The incidence of PJS is estimated between 1 in 8 300 and 1 in 280,000 [2].

The most characteristic and most frequent clinical manifestation is the freckling of the vermillion border and perioral region. The hyperpigmented spots may also be present on the eyelids, fingers and toes, around the nose, in the perianal and perivulval regions, as well as buccal mucosa. They develop during infancy and childhood, vary in size (from 1 to 5 mm in diameter) and have a tendency to fade with age. This sign, although very prevalent in patients with PJS, it is not a pathognomonic. It is also highly variable, from prominent to extremely subtle. It has no particular consequences to an individual's health but is quite helpful as a diagnostic feature [3].

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During the first and second decade of life, in nearly all individuals with PJS, hamartomatous polyps develop throughout the digestive tract. Most frequently they are located in the small bowel (96%), then the colon and stomach; they vary in size from 1 to 10 cm in diameter. The clinical picture is dominated by signs and symptoms of anaemia, rectal bleeding and non-specific abdominal pains. Nearly 50% of individuals with PJS experience recurrent small bowel obstruction and/or intussusception [4]. Currently, two methods of diagnosis and treatment of small intestine hamartomas are accepted: an intra-operative enteroscopy (IOE) and a double balloon enteroscopy (DBE). They allow for the resection of all polyps located in the small intestine [2]. Also, studies have demonstrated the chemopreventive efficacy of rapamycin on PJS [5, 6].

The histopathology of hamartomatous polyps in PJS is characteristic and diagnostic for the disorder. Moreover, apart from hamartomas, adenomas develop in the digestive tract of individuals with PJS and those tumours may undergo neoplastic transformation during adulthood. Colorectal cancer predominates as a malignancy seen in adults with PJS (lifetime risk of up to 39%), followed by an increased risk of pancreatic cancer (lifetime risk of 11–36%), female breast cancer (lifetime risk of 24–54%), gastric (29%), ovarian, small bowel, uterine and lung cancers [7]. Childhood malignancies associated with PJS include rare gonadal tumours: sex cord tumours with annular tubules (SCTAT) in girls and large-cell calcifying Sertoli cell tumours (LCTS) in boys [8, 9]. The criteria for PJS diagnosis are based on family history, histologically confirmed PJ polyps and characteristic mucocutaneous pigmentation [10].

Cowden syndrome

Cowden syndrome (CS), alongside Bannayan-Riley-Ruvalcaba syndrome (BRRS), belongs to an entity called PTEN hamartoma tumour syndrome (PHTS). CS was originally described by Lloyd and Dennis in 1963 and named after the reported patient, Rachel Cowden [11].

Cowden syndrome remains a clinical diagnosis and is based on consensus diagnostic criteria published (Eng C. PTEN hamartoma tumour syndrome 2001) and hence updated by the National Comprehensive Cancer Network (12). The criteria are divided into three categories: pathognomonic, major and minor. The pathognomonic criteria include mucocutaneous lesions, such as facial trichilemmomas, acral keratoses and mucosal papillomatosis, as well as adult Lhermitte-Duclos disease that is a cerebellar dysplastic gangliocytoma, a benign tumour of the cerebellum. Macrocephaly, non-medullary thyroid cancer, breast cancer and endometrial carcinoma constitute the group of four, major diagnostic criteria. Minor criteria are less specific but occur frequently, they include: thyroid lesions such as adenomas or a multinodular goitre, mild intellectual disability, lipomas, fibromas, fibrocystic disease of the breast, genitourinary tumours (especially renal cell carcinoma), uterine fibroids and hamartomatous intestinal polyps [12]. By the second decade of life, a significant majority of individuals with CS (80–90%) develop cutaneous and mucosal signs, however those are rarely a cause for medical concern [13]. A diagnosis of CS should be considered in children with macrocephaly and any of: developmental delay, dermatological features, vascular malformations or gastrointestinal hamartomatous polyps [14]. In adulthood, presentation of CS as a cancer predisposition syndrome becomes apparent. The lifetime risk of breast cancer for a female with CS is 85%, with penetrance of 50% by the age of 50. The lifetime risk for a non-medullary thyroid cancer is 35% with median age at diagnosis of 37 years; the lifetime risk for endometrial cancer is about 30% with the risk beginning in late 30s and early 40s. The above-mentioned cancers are included in the diagnosis as major criteria due to their incidence in CS, however the risk of other malignancies, such as renal carcinoma, colorectal cancer and melanoma is also increased, compared to overall population risk [11, 15, 16].

It has been reported that a pathogenic variant in the *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) gene had been found in up to 85% of individuals that fulfil the clinical diagnostic criteria for CS. Those pathogenic alterations include mostly point mutations in the coding region of the *PTEN* gene and flanking intronic sequences, mutations of the promoter region in about 10% of cases and rarely duplications/deletions of large portions of the gene [17].

Although the disorder is inherited in an autosomal dominant manner, a significant proportion of the cases are simplex (with no family history, caused by *de novo* mutations). The prevalence of the disorder is estimated as 1 in 200,000 births, however this is very likely an underestimation due to the fact that a significant number of individuals remain undiagnosed. It should be underlined that the clinical expression of a mutation in the *PTEN* gene is extremely variable, even in related individuals [17].

Juvenile polyposis syndrome

Juvenile polyposis syndrome (JPS) described by McColl et al. in 1964, is yet another syndrome characterised by the presence of hamartomatous polyps in the gastrointestinal tract [18]. The polyps histopathologically defined as juvenile, are characterised by hyperplasia of the mucous glands, retention cysts with oedema, obstruction of the glandular holes, profuse lamina and lack of smooth muscles [19]. Morphologically they vary in size (from a few mm to more than few cm) and shape: some are sessile, whereas others are pedunculated.

They begin to appear in the first decade of life and may be localised in the colon (98%), stomach (14%), duodenum (7%) and small intestine (7%) [20]. If sporadic, which is the most common situation, there is no increased risk of malignancy involved, however if multiple (the number varies between a few to one hundred), and with positive family history, it implies JPS through fulfilling one of the diagnostic criteria. The remaining diagnostic criteria (the Jass criteria) include: the pre-

sence of more than 5 juvenile polyps in the rectum and large intestine, or the presence of any number of juvenile polyps in the entire digestive tract. There are three clinical forms of JPS:

- juvenile polyposis of infancy that is associated with protein-losing enteropathy, additional anomalies and carries a poor prognosis,
- juvenile polyposis coli in which the polyps are limited to the colon only,
- generalized juvenile polyposis that refers to the presence of the polyps in the upper and lower digestive tract [21].

Clinically JPS presents as iron deficiency anaemia, abdominal pain, diarrhoea and/or rectal bleeding. In isolated cases, intussusception/intestinal obstruction or prolapse of a polyp were observed [22]. In more than 20% of individuals with JPS, various birth defects are detected both in the gastrointestinal tract (Meckel's diverticulum with umbilical fistula among others), and in other systems. The dysmorphic and/or extracolonic features include: pulmonary arteriovenous fistulae, ventricular septal defect, thoracic skeletal anomalies, undescended testes and hypospodias, renal agenesis and uterine defects, macrocephaly, telangiectasias, heamangiomata and lipomas [23].

In individuals with JPS, the risk of developing cancer increases, ranging from 9% to over 50%. The incidence of colorectal cancer is estimated at 17–22% by the age of 35 and 68% by the age of 60. The median age at diagnosis of colorectal cancer is 42 years. The incidence of stomach cancer is 21% in JPS patients with gastric polyps [24]. JPS is genetically heterogenous and caused by pathogenic variants in at least two genes: *SMAD4* (SMAD family member 4) and *BMPR1A* (bone morphogenetic protein receptor, type IA) are known to cause the phenotype. In both cases the inheritance pattern is autosomal dominant with about half of the cases attributed to *de novo* mutations with no family history of the disease. The frequency of JPS is estimated as 1 in 100,000 births [24].

Hereditary mixed polyposis syndrome

Hereditary mixed polyposis syndrome (HMPS) was first described in 1971 and concerned an 11-year-old girl with multiple juvenile polyps and adenomas of the colon and small intestine. In 1997, Whitelaw S.C. et al. proposed a name for this new condition that presented with atypical juvenile polyps, as well as adenomatous and hyperplastic polyps and named it hereditary mixed polyposis syndrome [25].

The clinical features of HMPS are presented in a multi-generation family, named St. Mark's family 96 (SM96). Among more than 200 members of this family, 42 showed different types of polyps, ranging from tubular adenomas, papillary adenomas and squamous adenomas, to hyperplastic polyps and atypical juvenile polyps [26]. In the histopathological examination, atypical juvenile polyps were a mosaic of hyperplastic polyps and adenomas. The mean age of diagnosis of HMPS patients in the SM96 family was 40 years [26]. Two three-generation families with a very similar course of the disease as in the SM96 family were described by Cao et al. [27]. Most frequently, the polyps were located in the large intestine. Affected family members had no extraintestinal manifestations [27]. It has also been found that individuals with HMPS show a significant predisposition to colorectal cancer development. There are no established criteria for diagnosing HMPS. It is rarely diagnosed before the age of thirty, unlike JPS, which most often affects children aged 5–15, when the number of juvenile polyps usually exceeds 50.

HMPS is inherited in an autosomal dominant manner, with some cases attributed to heterozygous duplication on chromosome 15q13-q14 that causes increased and ectopic expression of the *GREM1* (Gremlin 1) gene (HMPS 1) and in some cases is caused by heterozygous mutation in the *BMPR1A* gene [27, 28].

Conclusions

In cases of rare disorders with overlapping signs and different levels of cancer risks, genetic counselling and multi-specialist cooperation with the participation of a gastroenterologist, endocrinologist, dermatologist, neurologist, gynaecologist, oncologist and radiologist are extremely important. The goal of screening tests and imaging is prevention, early detection and treatment of the neoplasms that accompany those syndromes [29, 30].

Conflict of interest: none declared

Anna Kofla-Dłubacz
Wroclaw Medical University
Faculty of Medicine
2nd Department of Paediatrics, Gastroenterology and Nutrition
ul. M. Curie-Skłodowskiej 66
55-369 Wrocław, Poland
e-mail: anna.kofla-dlubacz@umw.edu.pl

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