Not all pediatric intestinal polyps are alike

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Abstract

***Background/Aims* : In childhood, clinical presentation of intestinal polyps is variable. Painless rectal red blood loss is the most common presenting sign. Most polyps are sporadic, isolated and benign. However, it is important to correctly identify exceptions. Rare inherited polyposis syndromes need to be recognized because of their increased risk of intestinal and extra-intestinal malignancies. Furthermore, a correct diagnosis and treatment of rare gastro-intestinal malignancies is crucial.**

***Methods* : Between 2016 and 2018 we encountered 4 different types of intestinal polyps. A database search was performed and patient files were checked for clinical manifestations and histopathology. Literature was searched to recapitulate red flags for these syndromes, probability of underlying genetic disorders and diagnostic criteria.**

***Results* : Between 2016 and 2018, 28 patients presented at the Ghent University Hospital with 30 juvenile polyps. Furthermore, we diagnosed juvenile polyposis syndrome, Li Fraumeni syndrome and familial adenomatous polyposis (FAP) in 1 patient each, whilst 2 FAP patients were in follow-up. Each of these diagnoses has a different lifetime risk of (extra)-intestinal malignancy and requires a different approach and follow-up. Histopathology and genetic testing play an important role in identifying these syndromes in pediatric patients.**

***Conclusion* : Although most intestinal polyps in childhood are benign juvenile polyps that require no follow-up, rare inherited syndromes should be considered and correctly diagnosed since adequate follow-up is necessary to reduce morbidity and mortality from both gastrointestinal and extraintestinal complications and malignancies.** (Acta gastroenterol. belg., **2020**, 83, **393-397**).

Key words : juvenile polyps, polyposis syndrome, FAP, Li Fraumeni, cancer predisposition.

Introduction

In children, colonic polyps are most frequently benign and do not carry the serious implications of polyps in adulthood. They occur in about 1% of children of which more than 90% are juvenile polyps. Recurrent painless red rectal bleeding without hemodynamic impact is the most common presenting symptom. In rare occasions transanal prolapse, intussusception and abdominal pain may also occur (1). On the other hand, painless red rectal bleeding without other symptoms isn't always a juvenile polyp (2).

Solitary juvenile polyps are most frequently diagnosed in the left colon between the age of 2 and 5 years, with a male predominance (3). Above the age of ten, simple juvenile polyps become less likely (4). Hereditary polyposis syndromes in children are rare, but should be considered and recognized because of the associated increased lifetime risk of (extra)-intestinal malignancy. The risk increases if polyps are present in larger numbers or are located outside the colon. Family history for polyps or early-onset colon cancer, physical examination looking for intestinal and extra-intestinal symptoms, endoscopic and pathology results as well as genetic analysis testing each play an important role in the diagnostic process.

Methods

Colonoscopies and oesophago-gastro-duodenoscopies, performed at the Ghent University Hospital between the beginning of 2016 and the end of 2018 in children from 0-16 years old, were evaluated to define all the patients diagnosed with intestinal polyps. Number of patients, newly diagnosed with or in follow-up for intestinal polyps, and the type of polyps are outlined. Four cases are described in detail. Literature was searched to recapitulate red flags for these syndromes, probability of underlying genetic disorders and diagnostic criteria.

Results

Database search

Between 2016 and 2018, 28 patients presented at the Ghent University Hospital were diagnosed with juvenile polyps. Two of them had a recurrence and one of them was a patient with Li-Fraumeni syndrome. Furthermore, we diagnosed juvenile polyposis syndrome, Li Fraumeni syndrome and familial adenomatous polyposis (FAP) in 1 patient each, whilst 2 FAP patients were in follow-up.

Cases

Case 1

A 1,5-year-old girl consulted for diarrhea, vomiting, fever, coughing, otorrhea and fatigue. She was known

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Submission date : 23/01/2020
Acceptance date : 18/02/2020

with mild pulmonary valve stenosis. Physical examination revealed pale mucosae, tachycardia and a systolic ejection heart murmur. She had a severe microcytic anemia (Hemoglobin 5g/dl). The fecal occult blood test was positive. The 99mTc pertechnetate Meckel scan was negative. An upper gastro-intestinal bleeding was postulated since no rectal bleeding was observed by the parents. Gastroduodenoscopy revealed a lobulated polypoid mass in the duodenum. A contrast computed tomography (CT) scan of the abdomen showed a 10 cm long jejuno-jejunal intussusception, starting at the angle of Treitz, with a mass bulging into the intestinal lumen. Explorative laparoscopy confirmed CT results and conversion to a mini-laparotomy was necessary to remove the mass using a wedge excision. Histopathological investigation revealed a polyp with prominent strands of smooth muscle cells, impossible to differentiate between a Peutz-Jeghers polyp and a juvenile polyp. Genetic testing for Peutz-Jeghers and juvenile polyposis syndrome were negative but she meets the diagnostic criteria for juvenile polyposis syndrome.

Case 2

An 11-year-old girl complained of four episodes of rectal red blood loss during defecation in the last months. There was no sign of constipation, abdominal pain or mucus discharge with stools. Family history was positive for intestinal cancer (paternal grandmother) and intestinal polyps (paternal aunt). A colonoscopy showed multiple (20-30) small flat polyps in the rectum and descending colon. Histopathological investigation showed tubular and villous adenomas with low-grade dysplasia. Genetic testing confirmed the suspicion of familial adenomatous polyposis with a de novo deletion in the APC gene. Because of a significant increase in the number of colonic polyps, a total colectomy with ileal pouch-anal anastomosis was performed two years later.

Case 3

A 12-year-old girl consulted because of rectal prolapse after defecation, sometimes needing pressure to reduce. There was also a history of hematochezia for which laxatives were started without effect. Anal inspection was normal. A picture taken by the parents was suggestive for a transanal prolapse of a rectal polyp. Two polyps (2cm and 0.5cm diameter) were resected during colonoscopy. The histopathological diagnosis was compatible with juvenile polyps.

Case 4

A 7-year-old boy known with autosomal dominant polycystic kidney disease and treated for right sided nephroblastoma at the age of one. He consulted at the emergency department because of intense abdominal pain and vomiting. Ultrasound revealed a colo-colonic intussusception with a lobulated, vascularized mass as pathological lead point. Enema reduction was not successful. An urgent abdominal MRI confirmed the ultrasound results. Colonoscopy revealed a large lobulated mass in the transverse colon. As complete endoscopic resection was impossible macro-biopsies were obtained revealing a high-grade sarcoma with rhabdomyoblastic/rhabdomyosarcomatous differentiation, compatible with the diagnosis of Triton tumor. The diagnosis was followed by a laparoscopy assisted extended right hemicolectomy with primary end-to-end anastomosis. Additional genetic testing confirmed Li-Fraumeni syndrome with a pathological TP53 mutation.

Discussion

Rare inherited intestinal polyposis syndromes such as FAP, Peutz-Jeghers syndrome, juvenile polyposis syndrome and PTEN (phosphatase and tensin homolog) hamartoma syndrome can manifest during childhood. Details concerning diagnostic criteria, clinical manifestation and genetics can be found in table 1.

Intestinal polyps are divided into 2 major categories based upon histology: adenomas (FAP) and hamartomas (juvenile polyp, juvenile polyposis syndrome, Peutz-Jeghers syndrome, PTEN). The most frequent encountered colonic polyp in childhood is the hamartomatous juvenile polyp. They are typically diagnosed between the age of two and five years, are located in the rectosigmoid in 84% or left colon in 11% and are solitary in 2/3 of the patients (5). In absence of a familial history and presence of less than 3-5 simultaneous juvenile polyps, they are considered to be benign and need no follow-up after endoscopic resection (4). Since juvenile polyps may be the first feature of juvenile polyposis syndrome, it is

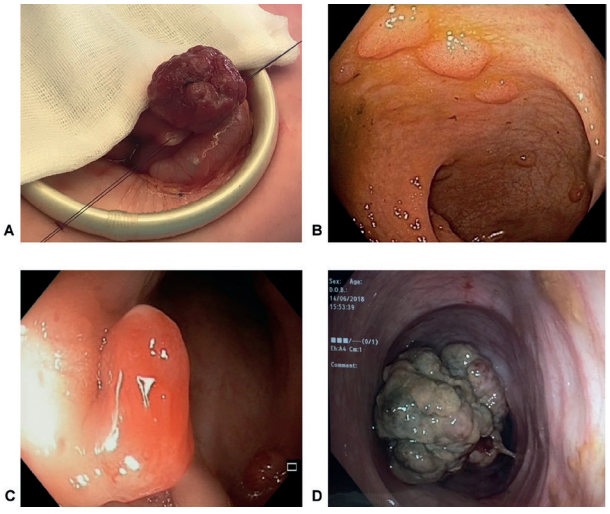

Figure 1. — (a) Surgical resection of jejunal polyp of case 1 with suspicion of juvenile polyposis syndrome (b) Endoscopic view of colonic tubular and villous adenomas of case 2 with FAP (c) Endoscopic view of colonic juvenile polyps of case 3 (d) Endoscopic view of Triton tumor of case 4 with Li-Fraumeni syndrome.

Table 1. — **Diagnostic criteria, clinical manifestations and genetics of hereditary intestinal polyposis syndromes**

	Diagnostic criteria	Clinical manifestation	Genetics
Familial adenomatous polyposis (1)	* ≥100 colorectal adenomatous polyps * APC mutation * Any colorectal adenoma + positive family history	* Colonic adenomas * Colorectal cancer * Gastric/ duodenal polyps, desmoid tumors, thyroidal & brain tumors, osteomas, congenital hypertrophy of the retinal pigmented epithelium, epidermoid cyst & supernumerary teeth	* Autosomal dominant * Affected gene: APC (5q21) * Found in 90-95% of patients (2)
Peutz-Jeghers syndrome (3)	* ≥ 2-3 hamartomatous polyps * ≥ 1 hamartomatous polyp + positive family history * Mucocutaneous melanosis + positive family history * Mucocutaneous melanosis + ≥1 hamartomatous polyp	* Mucocutaneous pigmented lesions * Gastrointestinal polyps * Increased risk of neoplasms * Extra-intestinal polyps: gallbladder, bronchi, bladder, ureter (4)	* Autosomal dominant * Affected gene : STK11 (LKB1) (19p13.3) * Found in 90-94% of patients (3)0
Juvenile polyposis syndrome	* >3-5 simultaneous colorectal juvenile polyps * Juvenile polyps throughout other GI tract * ≥1 juvenile polyp + positive family history (5)	* Juvenile polyposis of infancy: intestinal polyps, protein-loosing enteropathy, gastro-intestinal bleeding, diarrhea, intussusception, rectal prolapse, hypotonia, macrocephaly * Juvenile polyposis coli: colorectal polyps * Generalized juvenile polyposis: gastrointestinal polyps, colorectal cancer, skeletal/ cranial, vascular & cardiac abnormalities (6)	* Autosomal dominant * Affected gene: SMAD4 (18q21.1) or BMPR1A (10q23.2) * Found in 40% to 60% of patients (5)
Cowden syndrome	* Pathognomonic mucocutaneous lesions + 1 of the following: - ≥6 facial papules, of which≥ 3 trichilemmoma - Cutaneous facial papules + oral mucosal papillomatosis - Oral mucosal papillomatosis + acral keratosis - ≥6 palmo-plantar keratoses * ≥2 major criteria (see clinical manifestation) * 1 major + ³ 3 minor criteria * ³ 4 minor criteria (7)	* Major criteria: Breast cancer, epithelial thyroid cancer (nonmedullary), macrocephaly, endometrial carcinoma * Minor criteria: Other thyroid lesions (eg, adenoma, multinodular goiter), intellectual disability (Intelligence quotient < 75), hamartomatous intestinal polyps, fibrocystic disease of the breast, lipomas, fibromas, genitourinary tumors (especially renal cell carcinoma), genitourinary malformation, uterine fibroids * Facial trichilemomas, acral keratosis, papillomatous papules (8)	* Autosomal dominant * Affected gene: PTEN (10q23.31) * Found in 80% of the patients (7)
Bannayan-Riley-Ruvalcaba syndrome	Not yet established	* Hamartomatous polyps of GI tract * Increased risk of neoplasms * Developmental delay, macrocephaly, lipomas, hemangiomas, pigmented speckled macules of the glans penis, thyroid adenomas, Hashimoto's thyroiditis, lymphatic malformations, joint hyperextensibility, seizures, scoliosis, lipid storage myopathy and a high arched palate (9)	* Autosomal dominant * Affected gene: PTEN (10q23.31) * Found in 60% of the patients (7)

important to warn parents that if new symptoms arise, additional evaluation is indicated.

The rare juvenile polyposis syndrome (prevalence 1/100.000-160.000) should be considered in patients with a life-time total of ³ 5 colorectal juvenile polyps and/or juvenile polyps throughout the rest of the gastrointestinal tract and /or a familial history. Patients should be referred for genetic testing, although mutations in SMAD4 (18q21.1) or BMPR1A (10q23.2) are only found in 40-60% of patients (6). Extra-intestinal symptoms have been reported with a varying incidence. An overlap syndrome between juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia has also been described (6, 7).

Peutz-Jeghers syndrome (prevalence 1/200.000) is an autosomal dominant trait characterized by mucocutaneous melanosis and hamartomatous polyps with a typical frond-like or tree-like configuration, smooth muscle arborization and dilated crypts (7, 8). Patients should be referred for genetic testing when a typical Peutz-Jeghers polyp but also if only mucosal and lip freckling is present (not only for diagnostics for Peutz-Jeghers syndrome but also for other syndromes) (8).

PTEN hamartoma syndrome refers to a group of syndromes with different clinical presentation, caused by a germline mutations in the PTEN gene. Of these syndromes, Cowden syndrome (prevalence 1/200.000) and Bannayan-Riley-Ruvalcaba-syndrome (prevalence unknown) (BRRS) can manifest in the pediatric population. Both are characterized by multiple hamartomas and have many overlapping features. It has been suggested that they represent one condition but with variable expression and age-related penetrance (9). Pediatric Clinical Criteria for PTEN testing have been developed to identify children that should be referred to a geneticist. The criteria include macrocephaly (≥2 SD) and at least one of the following four additional criteria; autism or developmental delay, dermatologic features

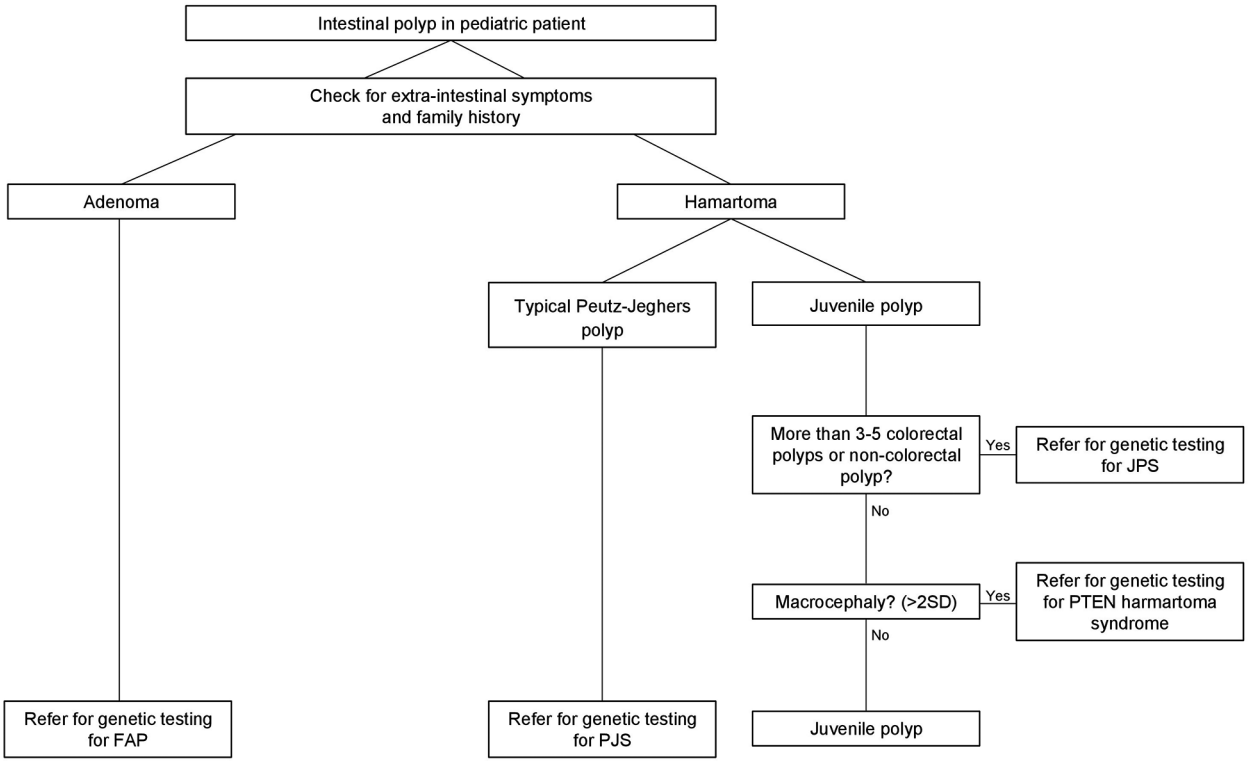

Figure 2. — Simplified flow diagram for referring patients with intestinal polyps.

(lipomas, trichilemmomas, oral papillomas, penile freckling), vascular features (such as arteriovenous malformations or hemangiomas), gastrointestinal polyps. Next to gastrointestinal hamartomatous polyps, also adenomas, ganglioneuromas and lymphoid follicles have been described. In addition, pediatric-onset thyroid cancer and germ cell tumors should indicate PTEN testing (10).

Colonic adenomas in children, regardless of the number, should always raise suspicion for FAP. This syndrome occurs in 1-3/10.000 individuals. Extra-intestinal symptoms should be excluded and the family should be referred for genetic testing. Attenuated familial adenomatous polyposis, a milder form of FAP, and MYH-associated polyposis also manifest with colonic adenomas but are less likely to present in childhood and are therefore not discussed in this paper (11).

Based on the previous information, we suggest a simplified flow diagram for referring patients with intestinal polyps in figure 2.

It is important to notice that the diagnosis of the previously mentioned hereditary polyposis syndromes can be made if a fitting germline mutation has been found or if the patient meets the diagnostic criteria (except for BRRS). The frequency of mutations found varies from 40 to 95% depending on the suspected diagnosis. Therefore, if there is a high clinical suspicion and negative genetic testing but the patient doesn't meet the criteria yet, active follow-up is indicated since the patient might meet the clinical criteria in the future if more symptoms arise.

Finally, if gastrointestinal polypoid structures are encountered especially if they display atypical features in size or aspect, malignancies originating from other structures (lymphoma, leiomyosarcoma, rhabdomyosarcoma, …) should be considered.

Conflict of interest

The authors of this publication did not receive any research or financial support. They also do not have any relationships that may pose conflict of interest.

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