Colonic polyps in children and adolescents

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Colonic polyps most commonly present with rectal bleeding in children. The isolated juvenile polyp is the most frequent kind of polyp identified in children. ‘Juvenile’ refers to the histological type of polyp and not the age of onset of the polyp. Adolescents and adults with multiple juvenile polyps are at a significant risk of intestinal cancer. The challenge for adult and pediatric gastroenterologists is determining the precise risk of colorectal cancer in patients with juvenile polyposis syndrome. Attenuated familial adenomatous polyposis (AFAP) can occur either by a mutation at the extreme ends of the adenomatous polyposis coli gene or by biallelic mutations in the MYH homologue (MYH) gene. The identification of MYH-associated polyposis as an autosomal recessive condition has important implications for screening and management strategies. Adult and pediatric gastroenterologists need to be aware of the underlying inheritance patterns of polyposis syndromes so that patients and their families can be adequately evaluated and managed. Colonic polyps, including isolated juvenile polyps, juvenile polyposis syndrome (JPS), familial adenomatous polyposis (FAP), AFAP and MYH-associated polyposis, are discussed in the present review.

Key Words: Familial adenomatous polyposis; Juvenile polyph; Juvenile polyposis syndrome; MYH-associated polyposis

Polypes du côlon chez les enfants et les adolescents

Les polypes du côlon se manifestent le plus fréquemment par des saignements rectaux chez les enfants. Le polype juvénile isolé est le type de polype le plus souvent observé chez les enfants. Précisons qu’ici, le terme ‘juvénile’ fait référence au type histologique du polype et non à l’âge du patient au moment de son développement. Les adolescents et les adultes qui présentent des polypes juvéniles multiples sont exposés à un risque important de cancer de l’intestin. Le défi, pour les gastro-entérologues qui œuvrent auprès des adultes et des enfants est de déterminer le risque précis de cancer colorectal chez les patients atteints du syndrome de polyposis juvénile. La polyposis adénomateuse familiale (PAF) atténuée peut apparaître à la suite d’une mutation aux extrémités du gène de la polyposis collique adénomateuse ou à la suite de mutations des deux allèles du gène MYH homologue (MYH). L’identification d’une polyposis associée au MYH comme maladie autosomique récessive a d’importantes répercussions sur les stratégies de dépistage et de prise en charge. Les gastro-entérologues auprès des adultes et des enfants doivent être au courant des modes de transmission héréditaire sous-jacents des syndromes de polyposis pour que les patients et leurs familles soient adéquatement évalués et traités. Les polypes du côlon, y compris les polyposis juvéniles isolés, le syndrome de polyposis juvénile, la PAF, la PAF atténuée et la polyposis associée au MYH, sont abordés dans la présente synthèse.

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children (including infants) present with failure to thrive, continue to accumulate during adulthood. In very rare cases, hood or in early adolescence with rectal bleeding. The polyps gastrointestinal (GI) tract. Patients usually present late in child-
multiple (more than five) juvenile polyps throughout the colon, or when there are multiple juvenile polyps in the colon, or when
JPS is an autosomal dominant condition characterized by multiple (more than five) juvenile polyps throughout the colon (4). Gastroenterologists should clinically suspect JPS when multiple polyps are found, the possibility of JPS is raised and a different management strategy is necessary. JPS is a autosomal dominant condition characterized by multiple (more than five) juvenile polyps throughout the colon (4). Gastroenterologists should clinically suspect JPS when

Solitary juvenile polyps carry no risk of intestinal cancer (2). The number of juvenile polyps is important because more than five polyps may carry implications for risk of CRC, which is discussed below. A challenge occurs when managing a patient with three or four juvenile polyps, because it is unclear whether the patient will develop the JPS phenotype (3) and therefore be at significant risk of intestinal cancer.

Colonoscopy with snare polypectomy and histological review is sufficient for management of isolated juvenile polyps. When there is a family history of juvenile polyps or when multiple polyps are found, the possibility of JPS is raised and a different management strategy is necessary.

JPS

JPS is an autosomal dominant condition characterized by multiple (more than five) juvenile polyps throughout the colon (4). Gastroenterologists should clinically suspect JPS when there are multiple juvenile polyps in the colon, or when juvenile polyps are found outside the colon. The polyps are mostly found in the colon but may occur throughout the gastrointestinal (GI) tract. Patients usually present late in childhood or in early adolescence with rectal bleeding. The polyps continue to accumulate during adulthood. In very rare cases, children (including infants) present with failure to thrive, anemia, hypoalbuminemia and abdominal pain secondary to large numbers of polyps throughout the GI tract. The histology of the polyps is characteristic of typical juvenile polyps as described above.

Investigators have tried to classify patients with multiple juvenile polyps into subgroups based on clinical presentation, with a diagnosis of either generalized juvenile polyposis (polyps throughout the GI tract), juvenile polyposis coli (polyps limited to the colon) and familial juvenile polyposis (juvenile polyps and a family history). When a patient has more than five juvenile polyps of the colorectum, juvenile polyps throughout the GI tract, or any number of juvenile polyps and a family history of juvenile polyposis (5), a JPS diagnosis should be considered.

Determining the precise cancer risk in children and adults with juvenile polyposis is a challenge. Family studies of juvenile polyposis suggest a 50% risk of developing GI cancer (5-7). CRC has been diagnosed in patients with juvenile polyposis as young as four years of age, although the mean age is in the third decade of life (6). The challenge is determining the risk of CRC in isolated individuals with multiple polyps (8). Genetic mutations, including SMAD4 (a transforming growth factor-beta intracellular signalling molecule) or BMPR1A, have been identified in 40% to 60% of patients with juvenile polyposis (4,9) (Table 1). An inactivating mutation in SMAD4 results in unopposed growth and polyp formation (Figure 3) (1). The mutant SMAD4 sequence predicts a truncated protein and absence of domains that are required for normal cellular functioning. Approximately 25% of newly diagnosed patients with JPS appear to have de novo or new mutations, with 75% exhibiting a family history (10).

Molecular genetic diagnosis may offer better predictors of cancer risk in children and adults with juvenile polyps. It is important for adult gastroenterologists following patients with juvenile polyposis to communicate that their offspring may be at risk of developing polyposis and subsequent GI cancer. Offspring presenting in their early teens or when symptoms occur should be considered for genetic testing when the disease-causing mutation is known in the family. Suggested surveillance includes colonoscopy every three years from the time of symptom occurrence or in the early teen years if symptoms have not occurred in the setting of a family history, and upper endoscopy every two years beginning at 15 years of age (4).

FAP

The majority of children and adolescents who are evaluated for FAP are identified in the context of a positive family history of FAP. This is because patients generally do not develop GI

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AFAP Attenuated Familial adenomatous polyposis; APC Adenomatous polyposis coli; MAP mutY homologue (MYH)-associated polyposis

Figure 1) Two-year-old boy presenting with a ‘prolapsing mass’. Colonoscopy revealed an isolated juvenile polyp which was removed by snare polypectomy. Histology confirmed a juvenile polyp

Figure 2) A pedunculated juvenile polyp on a long stalk identified in the sigmoid colon of a five-year-old girl presenting with a one-year history of intermittent, painless rectal bleeding

Table 1

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Symptoms until the third decade of life (mean age 33 years). Approximately 20% to 30% of FAP patients without a family history of the disease appear to have 'new mutations'. Thus, parents and siblings are not found to have the disease on investigation, but children of the affected person are at a 50% risk of the condition. The adenomatous polyposis coli (APC) gene is a large gene located on the long arm of chromosome 5 (Figure 4). The APC gene produces a large (2843 amino acids, 312 kDa) APC protein. Over 730 germline mutations have been identified; most of these are nonsense or frameshift mutations that result in a premature stop codon, thus producing a truncated, inactive APC protein. Current clinical screening recommendations for all first-degree relatives of patients with FAP include annual sigmoidoscopy beginning at 10 to 12 years of age (11). Most children with FAP have no GI symptoms. However, there are young children who present with hematochezia who have no family history of FAP and who are found to have a severe FAP phenotype (defined as greater than 1000 polyps) (12). Extracolonic tumours, both benign and malignant, can also occur, including hepatoblastoma, cystic osteomas of the jaw, desmoid tumours and multiple sebaceous cysts.

The link among hepatoblastoma, FAP, APC mutations and congenital hypertrophy of the retinal pigment epithelium is well established (13-17) The incidence of FAP in hepatoblastoma patients is approximately 100 times that in the general population. A major function of the APC gene is the downregulation of beta-catenin, a transcription-activating protein with oncogenic potential. APC mutations can alter this 'tumour suppressor' function, leading to an increased risk of hepatic malignancy and hepatoblastoma in particular (13). Hepatoblastomas typically affect children younger than three years of age and are the most common malignant liver tumours in children. Familial hepatoblastoma (siblings affected with hepatoblastoma) should raise the suspicion of an inherited APC mutation, warranting screening of parents for FAP (ophthalmological examination, colonoscopy and consideration of molecular studies). Sporadic hepatoblastoma appears to be associated with germline, rather than genomic APC mutations, in non-FAP families (13). Currently, no hepatoblastoma evidence-based screening guidelines are recommended for families with FAP.

This autosomal dominant disorder leads to the development of hundreds to thousands of adenomatous polyps in the colon (Figure 5). The average age of adenoma appearance is 16 years and the average age of colon cancer appearance is 39 years (10). Virtually all patients with FAP develop adenocarcinoma of the colon or rectum if left untreated, and therefore prophylactic colectomy is the standard of care. However, the timing of the colectomy is challenging and somewhat controversial. What is the risk of malignancy for the individually affected child? Peck et al (18) reviewed the available literature and identified 10 cases of cancer in FAP patients younger than 20 years of age. The youngest patient was five years old. Church et al (19) surveyed polyposis registries around the world to assess risk of CRC in children and teenagers with FAP. Among the 16 registries that responded, 14 patients younger than 20 years of age were identified with CRC. The youngest was nine years old. Nine of the 14 young patients with CRC had severe polyposis (defined as greater than 1000 colonic polyps) and one had mild polyposis. Church et al (19) calculated an estimated incidence of one case of CRC per 471 affected FAP patients younger than 20 years of age. However, gene mutations were not included in this study. Genotyping would have been interesting, because mutations in exon 15G classically result in a severe phenotype, which makes identification of these mutations relevant to patient management (20). In summary, cancer rarely occurs in FAP patients younger than 20 years of age and is usually associated with a severe polyposis phenotype.

Figure 3) Interruption of growth inhibitory signalling by a transforming growth factor-beta (TGF-β) by mutant Smad4. TGF-β signalling normally initiates cell cycle arrest and growth inhibition. In some kindreds with juvenile polyposis, a germline mutation in the TGF-β signalling protein, Smad4, interrupts growth inhibitory signalling by TGF-β, the result being unopposed growth and polyp formation. TGF-βRI/RII Transforming growth factor-beta receptor 1 / receptor 2. Reproduced/adapted with permission from Dr John Barnard, Children's Research Institute (Ohio, USA)

Figure 4) The anatomy of the adenomatous polyposis coli gene and its protein. Reproduced/adapted with permission from reference 46

Figure 5) Multiple adenomatous polyps identified at sigmoidoscopy in a 13-year-old boy being screened for familial adenomatous polyposis due to a maternal familial adenomatous polyposis history
TABLE 2

| Spigelman staging of duodenal polyposis in familial adenomatous polyposis |
|--------------------------|-----------------|
| Polyp number              | Points         |
| 1–4                      | 1              |
| 5–20                     | 2              |
| >20                      | 3              |
| **Histological type**    |                |
| Tubular polyp/ hyperplasia/inflammation | 1          |
| Tubulovillous             | 2              |
| Dysplasia                 |                |
| Mild                      | 1              |
| Moderate                  | 2              |
| Severe                    | 3              |
| **Stages**                |                |
| 0                         | 0              |
| I                         | 1–4            |
| II                        | 5–6            |
| III                       | 7–8            |
| IV                        | 9–12           |

Reproduced/adapted from reference 47

FAP, in 90% of families, arises from mutations of the APC gene (21). There is some correlation between the location of the mutation in the APC gene and the clinical phenotype of FAP (21,22). Extreme polyposis is observed when mutations are in the midportion of exon 15 (the central portion of the gene). Desmoid tumours and osteomas are more common with mutations in the distal portion of the gene (21).

Adenomatous duodenal polyps are common in FAP, with rates approaching 100% in patients who were followed over time (23-25). However, only a small fraction of affected patients develop invasive cancer (3% to 5%), because the progression of neoplasia in the duodenum of patients with FAP is slow (23,24). As a result, there is little evidence to support the initiation of upper GI surveillance in young children or adolescents with FAP (26). Current screening recommendations include upper endoscopy starting from 25 or 30 years of age (23), with the subsequent screening interval determined by the stage at baseline (27). Most FAP registries screen all FAP and attenuated FAP adults for duodenal adenomas, with aggressive interventional endoscopy at one- to five-year intervals (based on the Spigelman stage [Table 2]) and surgical resection reserved for severe cases (28).

Cyclooxygenase-2 inhibitors have shown promise in managing polyp burden in adult patients with FAP (29). During the development of a phase III pediatric trial of celecoxib and FAP, cardiovascular side effects were reported. Consequently, Health Canada removed FAP as an indication for celecoxib in December 2004, and thus, the drug is no longer available. Interestingly, no other country has followed suit.

AFAP

AFAP is a variant of FAP. Several distinct mutations within the APC gene have been associated with an attenuated phenotype and an autosomal dominant pattern of inheritance. Patients present with fewer colorectal polyps (less than 100, average 30), later onset of polyps and cancer, extracolonic manifestations and a predilection toward involvement of the proximal colon. Variability of phenotype expression within kindreds with identical mutations makes classification difficult (30). To date, at least 34 distinct mutations have been identified within the APC gene locus in individuals manifesting the attenuated FAP phenotype (31). Depending on the specific location of attenuated FAP mutation, varying phenotypic expression has been noted. Mutations at the 5’ end of the APC gene and within exon 9 are associated with fewer adenomas, whereas those at the 3’ end result in a more variable number of colorectal adenoma, and more severe upper GI manifestations (27).

Clinical surveillance in patients with AFAP may be based on the results of genetic testing. In individuals who test positive for a mutation associated with AFAP, baseline colonoscopy is recommended for those between 16 and 18 years of age (11). Early endoscopy is recommended due to the phenotypic variability seen within kindreds possessing identical mutations and the potential consequences of missing an early age of onset leading to a more diffuse polyposis phenotype. Screening with flexible sigmoidoscopy, the recommended modality for classic FAP (11), is inadequate because of the preponderance of right-sided lesions in AFAP. Patients with an APC mutation but negative endoscopic examination should undergo a repeat colonoscopy at 20 years of age. Patients who have colonoscopic findings consistent with AFAP should undergo polypectomy when feasible, followed by continued yearly surveillance.

Colectomy is advised when polyps are difficult to control colonoscopically (20 polyps or more; when one or more polyps show advanced characteristics, including size larger than 1 cm; or advanced histology). For patients with uninformative test results, the same recommendations apply, except that subsequent colonoscopy may be performed at two-year intervals. Upper endoscopy screening recommendations for AFAP are the same as for FAP and include upper endoscopy starting from 25 or 30 years of age (23).

Genetic testing for APC mutations should be considered in persons who exhibit typical FAP and also in persons with as few as 10 adenomas because of the possibility of AFAP (30). AFAP is not a distinct clinical entity and is a piece of the larger puzzle in the genetic predisposition to CRC (26). Large genotype-phenotype studies will help identify AFAP patients at greatest risk of CRC. Recent attention has focused on characterizing genetic predisposition to AFAP in individuals who do not have germline mutations in the APC gene.

MAP

MAP

Until recently, no other genetic causes had been described for the remainder of patients with FAP or AFAP. A second mechanistic explanation called MAP, an autosomal recessive condition, has been identified which has important implications for both screening and management strategies. In 2002, Al-Tassan et al (32) reported a family with recessive inheritance of multiple colorectal adenomatous polyps and carcinoma in three affected members of a single sibship. Until Al-Tassan’s discovery, no inherited defects of base excision repair had been associated with any human genetic disorder. Mutations of the genes mutM and mutY, which function in Escherichia coli base excision repair, led to increased transversions of guanine : cytosine to thiamine : adenine (33). Analysis of the human homologue of mutY, MYH, identified two missense variants – Y165C and G382D – in the affected subjects.
while unaffected siblings and the parents carried either heterozygous mutations or wild-type MYH sequences. APC mutations are detected in approximately 60% to 80% of classic FAP patients and in 10% to 30% of AFAP patients; MYH mutations are likely to account for about 10% and 20% to 25% of patients in these groups, respectively (34,35).

Genetic analysis of MYH should be offered to patients younger than 18 years of age with a phenotype resembling FAP or AFAP when no APC mutation is identified by genetic testing. Predictive genetic testing should be offered to siblings of patients found to have biallelic mutations to assess the need for endoscopic surveillance starting at 21 years of age. The current approach to children of biallelic carriers includes full gene screening of unaffected spouses to rule out heterozygous (or even asymptomatic biallelic) carriers, which may result in transmission of a biallelic state to offspring.

What is the significance of MYH mutations for children and adolescents? Sampson et al (36) studied 614 families with either presumptive or genetically confirmed FAP or AFAP in polyposis registries in the United Kingdom. The youngest case identified among the 25 patients with biallelic mutations of the MYH gene was a 13-year-old boy. This adolescent had more than 100 polyps and carried the two common MYH mutations (Y165C/G382D). This boy went on to develop gastric cancer at 17 years of age, suggesting the possibility of additional causative factors. This teenager is the youngest patient described with polyps and MYH biallelic mutations (36). The youngest MAP patient with CRC was a 21-year-old woman with 36 colonic polyps (37).

At Mount Sinai Hospital (Toronto, Ontario), we have screened five patients younger than 24 years of age presenting with CRC who had no detectable APC or hereditary nonpolyposis CRC mutations identified (38). No MYH mutations were identified. Thus, it appears that MYH mutations are not a common cause of multiple polyps in those presenting before 30 years of age. However, it must also be understood that to date, few patients younger than 18 years of age and diagnosed with adenomatous polyps or CRC have been screened for MYH mutations.

What is the management strategy for children and adolescents of parents with biallelic MYH mutations? Using statistical predictions, a carrier of two MYH mutations rarely produces children with a partner who also carries a heterozygous mutation (incidence of 1% to 2% of heterozygous MYH mutations in Caucasians) (39). In this case, the polyposis appears to be dominantly inherited in the offspring. Whether it makes sense to undertake genetic testing of the partners of patients with biallelic MYH mutations remains unclear. It will be of interest to evaluate teenagers and young adults with previously presumed AFAP for MYH mutations to determine the MYH phenotype, including the age of onset of polyposis along with the risk of adenomatous polyps and carcinoma. Furthermore, larger studies including adolescents and adults are necessary to help piece together the emerging MYH puzzle.

Most data on MYH suggest that the age at onset of polyposis is seen at a later stage in classic FAP, so initiating surveillance after 21 years of age seems reasonable (40). Further studies are required to assess the natural history of colorectal neoplasia in patients with MAP to guide surveillance intervals in adults and to make decisions regarding the timing of surgical interventions. While such studies are underway, most experts suggest that the clinical management of patients with biallelic mutations in MYH should be the same as for individuals with classic FAP.

As MYH screening becomes more widely available, pediatric gastroenterologists will be referred adolescents with MYH mutations identified as part of the evaluation of their affected parents. Adolescents with one MYH mutation do not require augmented screening colonscopy (38). For children and teenagers found to have biallelic MYH mutations, who were tested based on their parents or siblings, MYH status does not require upper endoscopy and colonscopy until 21 years of age (40). As prospective studies are completed, the precise lifetime risk of adenomatous polyps and CRC will be determined for obligate carriers.

**GENETIC COUNSELLING**

The importance of a thorough and accurate family history cannot be overstated. In most practices, a genetics consultation is probably necessary to assure collection of a sufficiently detailed family history and to assure that active efforts are made to collect relevant family medical records to verify verbal reports. The content of a genetics consultation provides the groundwork for any genetic testing that may eventually be offered (8). Because of the intensity and specialized nature of a genetic risk assessment, most physicians rely on a specialized centre with a multidisciplinary team.

The aim of polyposis registries is to promote the identification of relatives at risk of CRC and to ensure lifelong participation in surveillance programs. Another benefit of affiliation with a registry is access to specialty services such as prenatal counselling and support groups. Registries offer options for patient education, such as information pamphlets, and other age-appropriate visual aids (the registry at Mount Sinai Hospital has developed a child and adolescent friendly section, titled “Kids’ Korner”, on the registry Web site <www.mtsinai.on.ca/familialcancer>), which are useful adjuncts to genetic counselling. The decision to involve a child in the preparatory session is age- and maturity-dependent. Ideally, adolescents should be involved in the preparatory session so that they clearly understand the purpose and implications of genetic testing. Genetic counselling must also include an exploration of specific issues related to the family history and experiences with FAP (41). This may involve close personal involvement with relatives who have had cancer, variable screening experiences or surgical procedures. Family relationships can be profoundly affected by issues such as guilt and blame, and personal and familial identity may be strongly linked to FAP status. It is important to explore the perception of risk and its meaning, as well as the anticipated meaning of any test results. An essential task should be to determine whether the child has any psychologically damaging misperceptions regarding what having FAP and genetic testing itself means. The possibility of uninformative kindred testing, as well as the psychological implications for the patient and family, need to be discussed. Parents of at-risk minor children should devote time to discuss how and when test results and risks are to be communicated to the children.

Predictive genetic testing is now widely available for FAP and many FAP registries have adopted a policy of offering genetic testing at the onset of endoscopic screening. Genetic testing usually begins with an affected relative. The disease-producing mutation can be identified in approximately 80% of kindreds. Once the mutation is found in a person known to
have FAP, other at-risk family members can be tested for the presence or absence of the same mutation with approximately 100% accuracy (3). If the child is not found to carry the mutation, no clinical screening is required, although the child is, of course, still at the same risk of CRC as the general population. When genetic testing for the APC mutation in a family is uninformative (20% of cases), all at-risk relatives require endoscopic surveillance (11) beginning at 10 to 12 years of age. A survey involving 177 individuals tested for an APC mutation revealed that nearly one-third of uninformative genetic tests were misinterpreted by clinicians as a negative test result (42). Therefore, FAP families are best counselled and managed at specialty centres or by physicians with adequate education regarding the genetics of FAP.

**COMPLIANCE WITH SURVEILLANCE**

Many adolescents perceive bowel examination as an invasive procedure, and they may not comply with surveillance protocols. For parents, this process may reinforce latent fears, as indicated in a FAP adaptation study in which many parents expressed guilt about transmitting the mutant APC gene to their offspring (43). Parent information gaps or misperceptions may be mirrored in their offspring. Many children and adolescents benefit from a child-focused approach involving social workers, play therapists and specialized nurses experienced with issues related to FAP.

Many centres provide endoscopy in a pediatric endoscopy unit. This has helped to ensure that early screening experiences are seen in a positive manner because the subsequent annual examination is dependent on voluntary participation (44). We give adolescents and children some control by being encouraged to decide on their bowel preparation, choice of initial intravenous (propofol sedation or gas via mask sedation) and time of year that best suits their schedule for the endoscopy. It is important not to be zealous with overscreening of children and adolescents, because this may affect long-term compliance and trust in the health care system.

**FUTURE DIRECTIONS**

The majority of colonic polyps encountered in children and adolescents are benign lesions that are not associated with an underlying polyposis syndrome or risk of CRC. The challenge is identifying those patients who are developing a polyposis syndrome phenotype and therefore are at risk of CRC.

AFAP can occur either by a mutation at the extreme ends of the APC gene or by biallelic mutations in the MYH gene. The identification of MAP, as an autosomal recessive condition has important implications for screening and management strategies. Molecular genetic diagnosis and the discovery of mechanisms underlying polyp predisposition will allow for the development of more precise criteria for determining cancer risk in children and adults with multiple juvenile polyps (45). Adult and pediatric gastroenterologists need to be aware of the underlying inheritance patterns of polyposis syndromes so that patients and their families can be adequately evaluated and managed. Unquestionably, the future will bring the discovery of new genes that cause polyposis syndromes and contribute to the risk of developing cancer.

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