Screening and Surveillance Recommendations for Pediatric Gastrointestinal Polyposis Syndromes

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Abstract

Inherited polyposis syndromes are relatively rare disorders in pediatric gastroenterology practice, even in busy academic settings. It is important, however, for pediatric gastroenterologists to be aware of the serious health risks for children and their families who are affected by these disorders. The diagnosis of a polyp syndrome is often made in the first or second decade of life, long before the risk of gastrointestinal neoplasia. Pediatric gastroenterologists must be prepared then to offer families predictive genetic screening as well as endoscopic surveillance when appropriately indicated. The current overview is designed to provide general guidelines and, whenever possible, evidence-based recommendations for genetic testing, endoscopic surveillance and other screening approaches for children with inherited gastrointestinal polyposis syndromes. In this presentation, the focus is on screening for neoplastic change and complications in the gastrointestinal tract. It is important to understand that extraintestinal cancers are frequent in some of these disorders and the reader is referred to other authoritative sources for additional information about comprehensive health screening outside the gastrointestinal system [1].

Keywords

familial polyposis; adenoma; genetic screening

The Ethics of Genetic Testing for Polyposis Syndromes in Children

Genetic testing of children for an inherited polyposis syndrome in which the primary morbidity, gastrointestinal cancer, occurs many years later presents an ethical challenge for pediatric gastroenterologists [2]. Although discussion of all the ethical considerations is beyond the scope of this presentation, it is worth briefly contemplating some of the complexities of genetic testing in children and their families. Fortunately, inherited polyposis syndromes are single-gene autosomal dominant disorders with nearly complete penetrance and little known environmental effects. This somewhat simplifies the calculus for genetic testing and counseling. In most instances, specific treatment and prevention decisions may not be made contemporaneously with the results of genetic testing and the practical value of knowing results should be carefully considered before testing is undertaken.

In most societies, parents have the legal right to make decisions about health care for their children, including genetic testing, but certainly some adolescents have reached sufficient maturity and autonomy to be party to deliberations about testing. In some instances, an

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argument might be made to not reveal test results to children until they reach a legal age or a level of maturity that permits them to assimilate the information in a constructive manner.

There are risks and benefits of genetic screening of children and it is important to consider that some of these will likely occur at a point temporally remote from the potential morbidity of cancer. One potential benefit of early genetic testing is economic; that is, families can make plans for incurring the costs of care that may be nearly inevitable later in life. Studies generally show that children and families that test negative benefit by a decline in distress and anxiety, but this not uniformly the case, as up to 40% of families opt for ongoing endoscopic surveillance despite a negative genetic test result [3]. The risks to families and children who are found to be affected include anxiety, depression, loss of self esteem, stigmatization, and discrimination, all of which may pose significant morbidity.

When to test is an interesting consideration. A recent survey indicates that patients with familial adenomatous polyposis are at least willing to consider prenatal or preimplantation testing, but this is not commonly practiced. At the other extreme, some experts have suggested the "rule of earliest onset" which asserts that testing should be done no earlier than the age of first possible onset of cancer. No formal evidence-based guidelines exist on when to test. Because of the nuances in testing noted above, it is generally recommended that testing be conducted in consultation with an experienced genetic counselor. The best timing may vary from one family to another and the potential underlying diagnosis. In each section below, general recommendations are made, but should be individually considered for each family under consideration.

Familial Adenomatous Polyposis (FAP)

FAP, the most common inherited polyposis syndrome encountered in pediatric gastroenterology practice, is caused by a truncating mutation in the adenomatous polyposis (APC) gene [4]. The inheritance is autosomal dominant, although approximately 20-30% of cases are *de novo* mutations. The prevalence of FAP is about 1 in 10,000. The affected patient has 100s or 1000s of adenomatous polyps distributed throughout the colon. Fewer adenomas suggest attenuated polyposis (AFAP) or defects in the *MYH* gene. These two disorders will receive limited consideration in this discussion because studies to date indicate individuals with these defects rarely have intestinal lesions during childhood or adolescence.

The genotype

Wild-type APC is a tumor suppressor that functions as a negative regulator of the growth promoting Wnt signaling pathway. APC mutations in FAP have nearly 100% penetrance and can be identified by commercially available gene sequencing on a routine blood sample in more than 90% of affected kindreds. Dozens of truncating mutations leading to APC have been described and extensive genotype/phenotype correlations have been reported.

The phenotype

FAP is clinically heterogeneous, but the vast majority of children come to medical attention in the following two ways: presymptomatic presentation for genetic testing because of an affected family member has been identified, or presentation because of multiple colonic adenomas leading to rectal bleeding or related symptoms. The average age adenomas appear is 16 years.

Multiple FAP phenotypes exist, ranging from the milder phenotype in AFAP to specific clinical syndromes that were recognized long before APC mutations were identified. These include Gardner's syndrome in which colon adenomas occur in association with extraintestinal desmoid, dental, osteoid and epidermoid tumors, and Turcot's syndrome which includes

medulloblastomas, gliomas and ependymomas. Hepatoblastomas also occur with increased frequency in the setting of germline APC mutation.

From a genetic screening and endoscopic surveillance viewpoint, the most important phenotypic consideration is the nearly inevitable progression to colorectal cancer by the age of 50. Adenomas first appear at an average of 16 years of age and the average age of colorectal cancer at 39 years.

Genetic screening

Most experts recommend genetic testing for APC in at-risk patients just prior to 10-12 years, the age at which endoscopic surveillance is suggested. Should a specific APC mutation be identified within a family, then screening by DNA sequencing in a child can be undertaken with virtual certainty. The absence of a mutation effectively reduces colorectal cancer risk to that of the general population and the burden of endoscopic surveillance can be lifted. However, if an APC mutation is not identified in a FAP kindred, the diagnosis is not ruled out and an obligation for endoscopic surveillance remains. In patients with multiple colonic adenomas with no family history of FAP, genetic testing should be performed to detect a *de novo* mutation.

In APC mutation negative cases, one option is testing for *MYH* mutations, but no formal clinical recommendations for screening in children exist. In adults, it is expected that about 10% of APC mutation negative cases are *MYH* mutation positive; however, colonic adenomas and colorectal neoplasia are extremely uncommon in children with *MYH* mutations; thus, the discovery of *MYH* mutations in children will be quite rare.

Exceptions to the above recommendations may emerge with additional study. For example, in kindreds in which early and aggressive onset of colon adenomas occur, genetic screening during the first decade may be appropriate, especially if a mutation in APC codon 1309 exists. A rare scenario in which early genetic testing might be considered is in children with hepatoblastoma. This tumor is rare, occurring in about 1 in 1 million persons, but APC mutations can be identified in about 10% of cases. In addition, in known APC kindreds, the risk of hepatoblastoma is increased approximately 800-fold, leading some to recommend children undergo ultrasongraphy and alpha-fetoprotein screening protocols for 5-10 years, beginning at birth. Debate continues regarding the cost effectiveness of these screening and surveillance scenarios and no formal recommendations exist currently.

Endoscopic screening

Biannual endoscopic screening of at risk children generally should begin at age 10-12, unless early, aggressive disease has been observed in family members. Expert opinion suggests flexible sigmoidoscopy, since adenomas are numerous and distributed throughout the colon in most children. Once adenomas are identified, it is generally recommended that ileal pouch anal anastomosis or ileal anal anastomosis be performed.

Gastric and duodenal lesions occur in approximately 45% of children with APC. It is generally recommended that upper endoscopic surveillance begin when colonic adenomas are identified, or at age 20 to 25 years. Because of a risk of periampullary tumors, it is recommended that both end and side-viewing scopes be used. The risk for carcinoma in the proximal gastrointestinal tract is small, about 3-5%, and the occurrence during pediatric age group is rare. Screening every 1 to 5 years is suggested, depending on the number of lesions. Biopsies are done to assess for dysplasia.

Juvenile Polyposis

Juvenile polyposis is a rare autosomal dominant syndrome with an incidence of approximately 1 in 100,000. The underlying defect is an inactivating mutation in growth inhibitory transforming growth factor (TGF) β or bone morphogenetic protein (BMP) signaling pathways, leading to multiple gastric, small intestinal and colonic polyps.

The genotype

TGFβ and BMP signaling regulate epithelial cell growth inhibition and tissue morphogenesis. Defects in their signaling pathways leading to juvenile polyposis can be identified in 50 to 60% of cases if sophisticated techniques like multiplex ligation dependent probe amplification are used. Defects in Smad4, an intracellular protein common to both TGFβ and BMP pathways, are found in about 20% of juvenile polyposis cases. Defects in BMP receptor 1A (BMPR1A) are found in 20-25% of cases. Rarely, defects in ENG, also a TGFβ receptor, have also been identified.

The phenotype

Multiple juvenile polyps, usually 50-100, are found primarily in the colon, although small intestinal and gastric polyps are also observed. Occasionally a much smaller number of polyps are seen, as alluded to below. Proximal polyps are reported more commonly in the context of Smad4 mutations. An extremely rare infantile type characterized by extensive gastric polyposis, anemia and hypoproteinemia has also been described. Interestingly, several such patients have had deletions that encompass both PTEN and BMPRIA. ENG mutations are also associated with hereditary hemorrhagic telangiectasia (HHT), and coexistence of HHT and juvenile polyposis has been described.

The lifetime risk of colorectal neoplasia is about 50%, but neoplasia is very rare during childhood [5]. A predisposition to other malignancies is not proven in juvenile polyposis.

A precise clinical definition of juvenile polyposis has been proposed. This definition requires more than three to five colorectal juvenile polyps, juvenile polyps throughout the GI tract, or any number of polyps and a family history of juvenile polyposis. This definition is problematic as it is relatively common in pediatric gastroenterology practice to encounter children with multiple juvenile polyps (3 to 10 or more) with no apparent family history of juvenile polyposis.

Genetics screening

Since genetic lesions cannot currently be identified in about half of juvenile polyposis patients, genetic screening cannot be relied upon to establish a diagnosis, unless results are positive for a Smad4 or BMPR1A mutation. Additional research and discovery is required before routine clinical use of genetic screening in this disorder.

Endoscopic screening

Biannual or triennial colonoscopy and upper endoscopy is recommended beginning at about age 15 or earlier if polyps are clinically apparent. Because juvenile polyposis is rare and colorectal neoplasia in the pediatric age group is extremely uncommon, the evidence for these recommendations is limited.

PTEN Hamartoma Syndromes

Cowden's syndrome and Bannayan-Riley-Ruvalcaba syndrome are rare autosomal dominant, allelic variants of a defect in the phosphatase, tensin homologue deleted on chromosome ten

(PTEN) gene. The incidence is in the range of 1 in 200,000. Hamartomatous and juvenile polyps occur in the small intestine and colon, but the risk for gastrointestinal neoplasia is very low.

The genotype

PTEN is a dual specificity, protein/lipid phosphatase that modulates the phosphoinositol 3-kinase/AKT pathway, a key growth promoting signaling axis. About 90% of individuals with Cowden syndrome and 60% of patients with Bannayan-Riley-Ruvalcaba syndrome have a germline mutation in PTEN. Approximately 50% are *de novo* mutations.

The phenotype

Cowden syndrome is characterized by multiple hamartomas of the skin, breast, thyroid gland, endometrium and gastrointestinal tract. There is an increased risk of breast and thyroid neoplasia and other organs, although the risk of colon cancer is low and may not be more than the general population despite the presence of multiple gastrointestinal polyps. Other common findings are trichilemmomas and papillomatous papules, mild mental retardation and macrocephaly. Occasional children with autism and Cowden syndrome have been described. The gastrointestinal tumors are juvenile polyps, lipomas and ganglioneuromas. Specific clinical criteria have been developed for Cowden's syndrome. Bannayan-Riley-Ruvalcaba syndrome is characterized by multiple colonic juvenile polyps, macrocephaly, subcutaneous and visceral hemangiomas and lipomas, developmental delay, myopathy and pigmented penile lesions. There is no known risk for neoplasia in this syndrome.

Genetic screening

Genetic screening by DNA sequencing for PTEN mutations is widely available, but the pros and cons of testing in the pediatric interval should be carefully considered, as no specific modification of care is needed.

Endoscopic screening

No evidence-based, formal recommendations exist for surveillance of the gastrointestinal tract in children or adults with PTEN hamartoma syndromes.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is a rare, autosomal dominant hamartomatous polyp syndrome caused by a germline deletion in the LKB-1 (STK11) gene. The incidence is approximately 1 in 200,000. Hamartomatous polyps may occur throughout the intestinal tract. Because the syndrome is so rare, the evidence in support of specific screening and surveillance guideline are limited.

The genotype

The LKB-1 protein regulates programmed cell death, cell polarity, growth arrest and cellular energy metabolism. It also interacts with PTEN, the gene product mutation in PTEN hamartoma syndromes described below. At least 50% of patients with Peutz-Jeghers syndrome have a mutant LKB-1 gene, which can be detected by sequencing of DNA obtained from peripheral blood. Using more sophisticated approaches like multiplex ligation dependent probe amplification, mutations can be detected in as many as 90% of patients. *De novo* mutations occur in about 25%.

The phenotype

Most patients with Peutz-Jeghers syndrome have distinctive mucocutaneous pigmented macules on the lips and buccal mucosa. Multiple hamartomatous polyps occur throughout the

stomach, small intestinal and colon, commonly leading to recurrent abdominal pain due to intussusception. In fact, only about 40% of children with Peutz-Jeghers syndrome escape childhood without having had a laparotomy. The lifetime cancer risk is estimated at greater than 90%, with much of the cancer morbidity occurring outside the gastrointestinal tract and beyond the pediatric age group.

Genetic screening

In view of the distinctive clinical features of Peutz-Jeghers syndrome, genetic testing is of questionable importance in most cases. Some experts suggest that genetic screening may be helpful if symptoms have not occurred in the teenage years in at risk individuals in whom the kindred's genetic defect has been characterized.

Endoscopic screening

Endoscopic screening by colonoscopy is recommended every three years beginning when symptoms occur, or in early teenage years if symptoms have not occurred. Biannual upper gastrointestinal endoscopy and examination of the upper gastrointestinal tract by barium radiography are recommended beginning at about age 10. Numerous anecdotal reports of successful video capsule or double-balloon enteroscopy screening for small intestinal polyps have appeared in the literature in recent years, but no definitive recommendations on their use have been published. Polyps should be removed when technically feasible.

Acknowledgments

References

1. Schreibman IR, et al. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol 2005;100(2):476–90. [PubMed: 15667510]

2. Pelias MK. Genetic testing of children for adult-onset diseases: Is testing in the child'd best interests? The Mount Sinai Journal of Medicine 2006;73:605–608.

3. Douma KF, et al. Psychosocial issues in genetic testing for familial adenomatous polyposis: a review of the literature. Psychooncology 2008;17(8):737–45. [PubMed: 18613296]

4. Zbuk KM, Eng C. Hamartomatous polyposis syndromes. Nat Clin Pract Gastroenterol Hepatol 2007;4 (9):492–502. [PubMed: 17768394]

5. Brosens LA, et al. Risk of colorectal cancer in juvenile polyposis. Gut 2007;56(7):965–7. [PubMed: 17303595]