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EDITORIAL

Attenuated adenomatous polyposis of the large bowel: Present and future

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Abstract

Attenuated adenomatous polyposis (AAP) is a poorly understood syndrome, that can be defined as the presence of 10-99 synchronous adenomas in the large bowel, and it is considered a phenotypic variant of familial adenomatous polyposis (FAP). This definition has the advantage of simplicity, but it may include sporadic multiple adenomas of the large bowel at an extreme, or FAP cases on the other side. AAP shows a milder phenotype than FAP, with an older age of onset of adenomas and cancer, and less frequent extracolonic manifestations. AAP may be diagnosed as a single case in a family or, less frequently, it may be present in other family members, and it shows distinct pattern of inheritance. In less than 50% of cases, it may be caused by adenomatous polyposis coli (*APC*) or *MUTYH* mutations, referred to as *APC*-associated polyposis, inherited as an autosomal dominant trait, or *MUTYH*-associated polyposis, which shows an autosomal recessive mechanism of inheritance, respectively. Surveillance should rely on colonoscopy at regular intervals, with removal of adenomas and careful histological examination. When removal of polyps is not possible or advanced lesions are observed, the surgical approach is mandatory, being subtotal colectomy with ileo-rectal anastomosis the treatment of choice. Studies on this syndrome are lacking, and controversies are still present on many issues, thus, other clinical and genetic studies are requested.

Key words: Attenuated adenomatous polyposis; Genetic testing; Surveillance; Attenuated familial adenomatous polyposis; Adenomatous polyposis coli; *MUTYH*

Core tip: Attenuated adenomatous polyposis is a poorly understood syndrome, which may be defined as the presence of 10-99 synchronous adenomas in the large bowel, when at least 50% of the polyps removed are adenomatous. It is a variant of Familial Adenomatous Polyposis with a milder phenotype. In less than 50%

of cases, it is caused by adenomatous polyposis coli (*APC*) or *MUTYH* mutations, and less frequently by other genes. Surveillance should rely on colonoscopy at regular intervals, with removal of adenomas and careful histological examination. If removal of all polyps is not possible or advanced lesions are observed, the surgical treatment is mandatory.

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INTRODUCTION

Familial adenomatous polyposis (FAP) is a disease characterized by the presence of at least 100 adenomas of the large bowel, several extracolonic manifestations, and it is inherited as an autosomal dominant trait[1]. It is caused by constitutional mutations in the adenomatous polyposis coli (*APC*) gene[2,3], and, less frequently, by mutations in the *MUTYH* gene[4]. Attenuated familial adenomatous polyposis (AFAP) is considered a phenotypic variant of FAP, whose main feature is the presence in the large bowel of less than 100 synchronous adenomas[5]. "Attenuated" also means that the disease has a milder phenotype than the classical FAP. Indeed, patients with AFAP develop adenomas and cancer at an older age, and extracolonic manifestations are less frequent than in FAP[5,6]. Moreover, only one individual is affected in most families[7]. Nowadays AFAP may be included in the broad category of adenomatous polyposis syndromes[8].

The first approach to an attenuated adenomatous polyposis (AAP) should be clinical, and it is extremely important for the further management of the disease. The first step for a correct evaluation of patients with an intestinal polyposis must be a careful collection of the family history of cancers and premalignant lesions of the gastrointestinal tract, in order to get an estimate of the risk of an inherited predisposition to cancer. Particular attention should be paid to vertical transmission of the disease (from a generation to the next), sibling aggregation, and age at diagnosis of cancers in the family, especially for first- and second-degree relatives, although very often we are dealing with single cases in a family. Another milestone in the management is the particular attention that should be put on the histology of polyps removed in the large bowel. Polyps are usually adenomas, but it is not infrequent to find other histological variants (hyperplastic, serrated, hamartomatous, juvenile, or mixed), sometimes associated with adenomas. It is conceivable to define an adenomatous polyposis when more than 50% of polyps are adenomas, otherwise other polyposis syndromes should be taken into account[9]. Then, relying on the familial pedigree and on the characteristics of the individual phenotype of the proband, genetic testing for a germline mutation should be proposed to the proband, or to the most informative family members, when appropriate. In the case of attenuated adenomatous polyposis, firstly *APC* and *MUTYH* mutations should be searched for[8].

Indeed, constitutional mutations in *APC* or *MUTYH* genes were found in a large fraction of patients with AFAP[9-11]. Accordingly, now the term *APC*-associated polyposis (AFAP) can be more appropriately used when the *APC* gene is mutated, as in the classical FAP, whereas *MUTYH*-associated polyposis (MAP) is preferred when *MUTYH* mutations are found. However, many patients with AAP remains "genetic orphans", because at present, no constitutional mutation can be demonstrated[12,13]. Moreover, mutations in other genes can cause rare forms of attenuated polyposis[14].

As mentioned above, there is still controversy also on the morphology of polyps that should be included in the definition of attenuated polyposis. In fact, according to some authors, hyperplastic or serrated polyposis should be included in this category[15,16], considering the risk of developing colorectal cancer in these forms of intestinal polyposis[17]. Other polyposes have peculiar morphologic characteristics that allow to classify them as Hamartomatous polyposis syndromes (Peutz-Jeghers syndrome, Juvenile polyposis, and Cowden syndrome).

Thus, the picture is far to be completely elucidated, and, despite attempts to refine diagnostic accuracy, AFAP still remains poorly understood and defined. We think that, before proceeding toward the genetic diagnosis, it is mandatory to try to reach a useful definition of the syndrome that we prefer to refer to as AAP. Probably one possible definition is to consider as AAP any patient with synchronous adenomas of the large bowel ranging between 10 and 99, not considering age of onset, other clinical features, or formal and molecular genetics. Of course this definition is totally clinical, and, as all definitions, it reflects only part of the truth. For example, near the upper and lower limits of 10 and 99 adenomas it is impossible to sharply cut off sporadic multiple adenomas for the lower limit, and classical FAP for the upper. Moreover, we do not know whether the development of further metachronous adenomas during surveillance of patients may change the definition and the management of the syndrome. Another controversial issue is the presence in the family of other patients with adenomas or cancer[10]. However this definition has the advantage of simplicity, and it allows to have a solid ground on which rely for the genetic and clinical management of affected patients and family members. Another issue is the fraction of adenomas on the total number of polyps necessary to define an adenomatous polyposis. We think that at least 50% histologically confirmed adenomas are necessary for the definition of AAP[9].

Since the definition is unclear and there is no real consensus, incidence and frequency of AAP are difficult to establish. Frequency may be estimated to be less than 15% of all adenomatous polyposes, but a systematic search for AAP has never been carried out. As mentioned above, the age of onset of AAP is delayed as compared with FAP[5,9], adenomas seem more prevalent in the proximal colon[18,19], to spare the rectum[20], and they tend to be flat[21,22], and sometimes also hyperplastic polyps and flat serrated adenomas are present[23]. The risk of developing cancer is not 100% as in classical FAP. Extracolonic manifestations [duodenal adenomas, periampullary carcinoma, desmoid tumors, osteomas, epidermoid cysts, congenital hypertrophy of the retinal pigmented epithelium (CHRPE), supernumerary teeth, thyroid carcinoma, and hepatoblastoma] seem less frequent than in FAP, though studies are very few on this topic[23,24].

As mentioned, genetic testing should be offered to patients with AAP. *APC* and *MUTYH* are the two genes most frequently involved in the pathogenesis of AAP. However, constitutional mutations of other known and unknown genes contribute to the AAP phenotype.

APC is a tumor-suppressor gene, located on the long arm of chromosome 5[25]. In classical FAP a mutated allele is inherited, the other allele is damaged or lost by a somatic event, and this allows the growth of adenomas. Then, other mutational events in other genes are required to push ahead the malignant transformation. Some correlations between the site of the mutations within the open reading frame of the gene and the clinical manifestations of the disease have been reported so far (the so-called genotype-phenotype correlations)[26]. As far as AAP is concerned, the overall frequency of *APC* mutations is difficult to establish, however it can be estimated around 10%-20% of patients with less than 100 adenomas[9]. In these cases, AAP (namely AFAP) is inherited as an autosomal dominant disease, as it happens for classical FAP. In AAP, we know that *APC* mutations are found mostly near the 5' and 3' ends of the gene, and sometimes on exon 9[7,26], but other regions of the gene can be mutated.

MUTYH is a base excision repair gene whose protein repairs oxidative damage to DNA[4]. Biallelic mutations of that gene cause CG-AT transversions in several other genes, including *APC* and *RAS*. The two most frequent mutations found in patients with AAP are Y179C and G396D, both missense[27]. Thus, *MUTYH*-associated polyposis (MAP) has a recessive pattern of inheritance, and it is particularly frequent in patients with less than 100 adenomas[28,29], though *MUTYH* mutations may be found also in a small fraction of patients with classical FAP and no *APC* mutation[28]. It can be estimated that *MUTYH* is mutated in 20%-40% of patients with AAP[12,29]. Mean age at diagnosis seems delayed, when compared with patients with *APC* mutations[30]. Mutations in one allele only of the *MUTYH* gene seem not to confer a higher risk of developing intestinal adenomatous polyposis.

Recently, other genes that may be constitutionally mutated in intestinal polyposis syndromes, were found associated with the AAP phenotype. These genes, involved in DNA synthesis are polymerase D1 (*POLD1*) and polymerase E gene (*POLE*). Mutations in one of these genes cause the rare Polymerase Proofreading-Associated Polyposis (PPAP)[14], which is inherited as an autosomal dominant trait. Mutations in these genes have been reported so far also for Lynch syndrome, and probably cause an excess also of brain tumors[31].

Constitutional mutations in other genes may explain a certain fraction of AAP: *NTHL1*[32], *MSH3*[33], *FOCAD*[34], *POLD3* or other polymerase genes[35]. In the near future, other genes will be discovered in the germline of patients with AAP.

No established guidelines exist for the management of AAP. When a mutation is found in *APC* or *MUTYH* (biallelic), a colonoscopy should be carried out, beginning at puberty, along with esophago-gastroduodenoscopy, and repeated over time every 2-3 years, and then regularly. However, since the genetic test is often negative for constitutional mutation, management is empirical and based on clinical findings in most cases. The choice of following a patient endoscopically or with a surgical approach is a matter of debate. The more convenient program is to continue an endoscopic follow-up when all polyps can be removed during colonoscopy, and to counsel surgery when the number of polyps is high or with multiple diminutive polyps, or in case of low compliance, or when a severe dysplasia or cancer is found at histological examination in one or more polyps[8,36]. When surgery is necessary, and the rectum is spared by polyps, a subtotal colectomy with ileo-rectal anastomosis is the treatment of choice[37]. Sometimes, when a severe phenotype (profuse polyposis) is present, due to mutations in particular zones of the genes, the surgical resection should be enlarged[38,39]. At variance with FAP, no valuable information is available for chemoprevention with non-steroidal anti-inflammatory or other drugs in AAP, though the smaller number of polyps might be an advantage. Surveillance for upper gastrointestinal lesions (gastric polyps and duodenal/jejunal adenomas) with gastroduodenoscopy may be recommended at lapses of time guided by the Spigelman' stage of duodenal polyposis, as in FAP, but no data are available at the moment[8].

CONCLUSION

In conclusion, AAP is a poorly defined syndrome which deserves further research. It may be defined as the presence of 10-99 synchronous adenomas in the large bowel, when at least 50% of the polyps removed are adenomatous (otherwise other polyposis syndromes should be suspected). This definition has the advantage of simplicity, but it may include sporadic

multiple adenomas of the large bowel at an extreme, or FAP cases at the upper limit. AAP shows a milder phenotype than FAP, with an older age of onset of adenomas and cancer, and less frequent extracolonic manifestations. AAP may be diagnosed as a single case in a family or, less frequently, it may be present in other family members. In less than 50% of cases, it may be caused by *APC* or *MUTYH* mutations, referred to as *APC*-associated polyposis (AFAP), or *MUTYH*-associated polyposis (MAP), respectively. Surveillance should rely on colonoscopy at regular intervals, with removal of adenomas and careful histological examination. If removal of all polyps is not possible or advanced lesions are observed, the surgical treatment is mandatory. With no doubt, we need further insights into the undefined and poorly understood issue of AAP.

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