The role of mutation analysis of the APC gene in the management of FAP patients. A controversial issue

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BACKGROUND: *A correlation between the location of mutation in the adenomatous polyposis coli (APC) gene and clinical manifestations of familial adenomatous polyposis (FAP) has repeatedly been reported. Some Authors suggest the use of mutational analysis as a guide to select the best surgical option in FAP patients. However, data coming from studies on large series have raised questions on this issue. The aim of this study is to discuss the role of the genetic tests in the management of FAP.*
METHODS: *A literature review was performed considering only peer-reviewed articles published between 1991-2015. All the studies examined the role of genetic as a guide for surgical management of FAP.*
RESULTS: *Of 363 articles identified, 21 were selected for full-text review. We found different positions with regard the use of genetic tests to determine surgical management of FAP. In particular, while consistent correlations between the APC mutation site and FAP phenotype were observed in large series, 8 studies reported a wide variation of genotype-phenotype correlation in patients with the same mutation and they recommended that decisions regarding surgical strategy should be based not only on genotype but also on the clinical factors and the will of the patient who must be fully informed.*
CONCLUSIONS: *The decision on the type and the timing of surgery should be based on the assessment of many factors and genotype assessment should be used in combination with clinical data.*

KEY WORDS: Disease severity, Familial adenomatous polyposis, Genetic tests, Genotype-phenotype correlations, Surgical management

Background

Familial Adenomatous Polyposis (FAP) is an autosomal dominant disease which is classically characterized by the development of hundreds to thousands of adenomas in the rectum and colon during the second decade of life. Almost all patients will develop a colorectal cancer if they are not identified and treated at an early stage. The severity of the FAP phenotype is traditionally classified on the basis of the number of polyps in the large bowel. Patients with a severe phenotype (>1000 adenomas) have an higher risk to present a colorectal cancer at the time of diagnosis [1-3]. Several extracolonic manifestations (ECM) have been observed, such as upper gastrointestinal tumors, desmoid tumors, osteomas, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermoid cysts, as well as some extra-intestinal malignancies (cancers of thyroid, brain, pancreas and hepatobiliary tract). These manifestations can influence survival of FAP patients as much as the severity of colorectal polyposis.

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Germline mutations in the adenomatous polyposis coli (APC) gene are responsible for FAP. APC gene was identified in 1991 and since then a correlation between the location of APC mutation and clinical manifestations, including both colonic and extracolonic ones, has repeatedly been reported [4-10]. Treatment of colorectal disease is mainly surgery and we have two options: subtotal colectomy with ileorectal anastomosis (IRA) and total proctocolectomy with ileo pouch/anal anastomosis (IPAA). IRA is a simpler procedure with better functional outcomes but it is associated with higher risk of cancer in the rectal stump. Wu et al [11] showed that mutations at codon 1309 and 1328 in exon 15G were related to a severe colorectal polyposis. They also found that of 43 patients undergone IRA, the rectum was later removed in eight. Seven of these patients had a mutation at codon 1309 and 1328. Vasen et al [12] had already recommended the usage of mutational analysis as a guide to select the best surgical option in FAP patients. In fact, they proposed performing ileorectal anastomosis for patients with mutation before codon 1250 and proctocolectomy with ileo pouch-anal anastomosis (IPAA) in those patients having APC mutation located beyond codon 1250 . However, other researchers have criticized this recommendation, finding data that make this issue more complex and controversial [13,14].

We aim to show the pros and cons of the mutational analysis in surgical decision-making, to compare the different experiences coming from studies on large series and thus to discuss whether this tool should be used alone or included in a comprehensive evaluation taking into account several factors.

Methods

A literature review was performed considering only peer-reviewed articles published between 1991-2015. All the studies examined the role of genetic as a guide for surgical management of FAP. The terms used for the research were: familial adenomatous polyposis, adenomatous polyposis coli genotype, genotype-phenotype correlation, polyp burden, desmoids, extracolonic manifestations, severity of FAP, multi-tumoral syndrome. Case reports or studies on series of less than 10 patients were excluded.

Results

We found 363 articles using the search terms reported above. Firstly, we selected the articles on the basis of the title. 79 articles, whose title was relevant, were assessed by reading the abstracts and, finally, 21 articles[10-30] were submitted to a full-text review. We found different positions with regard the use of genetic tests to determine surgical management of FAP. In particular, while consistent correlations between the APC mutation site and FAP phenotype were observed in large series (Table I), 8 studies [10,13,23,25-29] reported a wide variation of genotype-phenotype correlation in patients with the same mutation and they recommended that decisions regarding surgical strategy should be based not only on genotype but also on the clinical factors (mainly the age of the patient, severity of colonic polyposis, the risk to develop desmoids and the wish to have children) and the will of the patient who must be fully informed.

Discussion

Genotype-Phenotype Correlations

Several Authors have demonstrated that the severity of colorectal polyposis is correlated with the site of the mutations in the APC gene [10-16]. Colorectal polyposis is classified as follows: profuse, intermediate and attenuated. Profuse polyposis is characterized by development of thousands of polyps at young age (first and second decade of life). Patients with the intermediate form develop hundreds to thousands of colorectal polyps in their second and third decades of life. In the attenuated FAP (AFAP) patients have fewer than 100 polyps and cancer onset is delayed. Mutations between 1250-1464 are associated with profuse polyposis, while mutations related to intermediate polyposis occur between exon 5 and the 5' portion of exon 15. Mutations determining AFAP tend to cluster in the extreme 5' portion of the gene (exons

Table I - *Reported genotype-phenotype correlations in FAP*

Phenotype	Codon no.	Authors (References)
Profuse polyposis	1250-1464	Nagase[16] 1992, Bertario[30] 2003
	1309	Caspari[17] 1995
Intermediate	157-1595	Nagase[16] 1992
Attenuated (AFAP)	Exons 3,4,5 and 9	Spirio[15] 1993
Desmoid tumors	1445-1578	Caspari[17] 1995
CHRPE	463-1387	Olshwang[18] 1993
Thyroid carcinoma	5' to 1220	Cetta[19] 2000

3,4,5) and in the alternatively spliced region of exon 9. Further studies have found that genotype-phenotype correlations are not restricted to the number of colonic polyps, but also concern the occurrence of extracolonic manifestations. In fact, Caspari et al. [17] demonstrated that mutations beyond codon 1444 are associated with the development of desmoid tumors. In addition to this, Olschwang et al [1] have shown that in FAP patients with mutations in codons 136-302 of the APC gene, congenital hypertrophy of the retinal pigment epithelium (CHRPE) does not develop, while in those with mutations between codons 463-1387 regularly does. Other genotype-phenotype correlations were observed by Cetta et al [19], who claimed that a thyroid cancer was associated with mutations at 5' of the APC gene to codon 1220. In particular, they reported interesting data on genetic alterations in thyroid carcinoma related to familial adenomatous polyposis, which could have clinical implications. Their data highlight that 1) FAP- associated thyroid cancer has an high incidence of ret-PTC activation in the tumoral tissue and 2) despite multicentricity and early lymph node involvement, FAP-associated thyroid cancers usually have an excellent prognosis, so that hyperradical procedures are unnecessary. Cetta et al also found that hepatoblastoma is more frequent in patients with mutations in exon 15, however it was also observed in patients with mutations in the 5' portion of the APC gene at codons 141, 215, 302 and 541 [20,21]. No large study has been conducted on the correlation between APC mutation site and duodenal tumors.

It is also debated the criterion to define the severity of FAP by the number of adenomas in the large bowel. Debinski et al. [22] demonstrated that a resected specimen with > 1000 polyps has double the chance of containing a cancer compared with one with <1000 polyps. In 1992 a correlation between genotype and severity of colorectal polyposis was described; a profuse polyposis was observed in patients with a truncating mutation between codons 1250 and 1464. As reported above, Wu et al started from these observations to suggest removing the rectum from the beginning and performing ileopouch anastomosis for patients with APC germline mutations between codons 1250 and 1464 region, that is defined as mutation cluster region (MCR). However, Cetta et al. [23] contended that the severity of the disease cannot be determined solely on the basis of the number of colonic polyps, given that FAP is a genetically determined multitumoral syndrome. In fact, FAP patients with the APC mutation at codon 1061 can have a high incidence of both thyroid carcinoma and hepatoblastoma; both tumors can occur before the development of colon cancer and also before the occurrence of colonic polyps. In particular, hepatoblastoma can be lethal during childhood. What's more, some Authors [23-25] reported that three peculiar extracolonic manifestations (brain tumors, papillary thyroid carcinoma and hepatoblastoma) may be present together in some patients or in patients belonging to the same kindred. These patients had mutations in the 5' portion of the APC gene, but almost always outside of MCR. Most of these patients also showed CHRPE and they developed brain or liver tumors before the occurrence of colonic polyps. These observations need further confirmation but they could facilitate early diagnosis, better treatment and a deeper understanding of genotype-phenotype correlations both of colonic and extracolonic manifestations.

Genetic Tests in Surgical Management of FAP

Several Authors have proposed the use of mutational analysis to guide the surgical management of FAP patients. However, a wide phenotypic variability has been observed among patients with the same APC mutation. Modifiers genes and environmental factors may play important roles in the occurrence of the colonic and extracolonic manifestations. In fact, a study has found that the ATP5A1 gene (chromosome 18q21) may act as a modifier gene in the development of CRC in the murine version of human FAP (APCMin mice). The gene has previously been demonstrated to suppress polyp formation in mice when it is mutated, with mutant Atp5a1 mice having a reduction in small intestinal and colonic polyps by approximately 90%. Surprisingly, more adenomas progress to carcinomas in Min mice with the Atp5a1 mutation [25,26]. However, clinical inferences sometime seem to be justified as in the case of FAP-associated thyroid carcinomas which show a high incidence of ret-PTC activation in the tumour tissue. Thyroid tumors with this genetic alteration usually show indolent behaviour, which suggests that hyperradical operations should be avoided.

Friedl et al. [27] also reported a consistent correlation between the site of mutation in the APC gene and severity of intestinal polyposis or presence of clinically relevant extracolonic features, in a large series of 680 FAP patients. However, the results of their study demonstrated a wide variation with regard to both age at onset of intestinal symptoms and development of CRC even in patients with the same mutation. They recommended that decisions regarding the individual patients should be based not only on the genotype, but also on the colonic phenotype. However, a higher incidence of desmoid tumours in patients with mutations located at 3' of codon 1444 compared with patients with mutations at 5' of this codon has consistently been reported by several authors. Nevertheless, not all patients with mutations from 3' to codon 1444 developed clinical desmoid disease although a subclinical manifestation cannot be excluded. Desmoids may develop particularly after surgical intervention. As at least 60% of patients with mutations within codons 1445-1580 develop desmoids, it seems advisable to postpone elective colectomy in

patients with such mutations until disease progression in the colon is substantial. In view of these observations, genetic testing as well as the family history of desmoid tumors can be useful to identify patients at high risk to develop desmoids tumors after surgery [27-30].

Conclusions

There are strong arguments in favour of a correlation between the location of the mutation on the APC gene and the phenotype of FAP manifestations as well as the severity of the syndrome.
In fact, it has been attempted to categorize the phenotype according to severity of the polyposis and the associated site of mutation on the APC gene.
However, because of wide variety of genotype-phenotype correlation, the knowledge of the germline mutation cannot be used as the only factor to choose the best management for every FAP patient, but it can be helpful in some difficult decisions concerning the age to begin endoscopic surveillance, the intensity of rectal endoscopic follow-up as well as the management of some extracolonic tumors like FAP-associated thyroid carcinoma. In our clinical practice we prefer to include the genotype assessment in a comprehensive evaluation considering clinical data and the will of the patient who must be fully informed.
Moreover, due to the complex pathogenesis as well as the heterogeneous natural history of this syndrome, we claim the importance of a multidisciplinary approach in decision-making of FAP management by involving geneticists, clinicians, endoscopists and surgeons.

Riassunto

INTRODUZIONE: Una correlazione tra la sede della mutazione nel gene APC (Adenomatosis Polyposis Coli) e le manifestazioni cliniche della FAP (familial adenomatosis polyposis) è stata riportata da più studi.
Alcuni Autori raccomandano l'uso dell'analisi mutazionale per la scelta della migliore strategia chirurgica nei pazienti FAP sia per il tipo di intervento che per il timing. Comunque, i dati provenienti da studi su ampie casistiche hanno messo in discussione questa raccomandazione. L'obiettivo del presente articolo è quello di discutere il ruolo dei test genetici nel decision making della FAP.
METODI: Una revisione della letteratura è stata realizzata considerando gli articoli pubblicati tra il 1991 e il 2015 in Pubmed. Tutti gli studi trovati esaminano il ruolo della genetica come guida per la strategia chirurgica nella FAP.
RISULTATI: Dei 363 articoli identificati, 21 sono stati selezionati sulla base dei criteri di inclusione.
Le due principali opzioni chirurgiche per la FAP sono: la colectomia con ileo-retto anastomosi (IRA) e la proctocolectomia restaurativa con anastomosi ileo-anale su pouch (IPAA).
Abbiamo evidenziato differenti posizioni relativamente all' uso dei test genetici per determinare la gestione chirurgica della FAP. In particolare, mentre è stata riportata in ampie casistiche una significativa associazione tra il sito della mutazione nel gene APC e il fenotipo della FAP, otto studi hanno evidenziato una notevole variabilità nella correlazione genotipo-fenotipo in pazienti con la stessa mutazione e proponevano che la decisione sulla migliore gestione del paziente FAP non fosse solo basata sul genotipo ma anche sui criteri clinici e sulla volontà del paziente che deve essere pienamente informato.
CONCLUSIONI: La decisione sul tipo di intervento e sul timing appropriato dovrebbe essere basata su molti fattori e l' analisi mutazionale dovrebbe essere usata in associazione ai dati clinici.

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