Familial adenomatous polyposis

Key facts

- Familial adenomatous polyposis (FAP) is an autosomal dominant condition, resulting in an extremely high risk of colorectal cancer, together with other characteristic manifestations.
- This is a rare condition, affecting approximately 1 in 8,000 individuals.
- The main clinical feature is the development of hundreds to thousands of adenomatous polyps in the large bowel during adolescence, with virtually inevitable progression to cancer by the late 40s.
- In nearly all affected people, prophylactic surgery to remove most or all of the large bowel is needed to prevent colorectal cancer.
- Lifelong surveillance is required to manage the cancer risk in any remaining large bowel, and in the upper GI tract.

Clinical features

- Usually over 100 (and sometimes several thousand) adenomatous polyps develop in the large bowel, usually during teenage years. These inevitably progress to colorectal cancer unless prophylactic surgery is undertaken.
- Most individuals with FAP develop duodenal adenomas, with around 10% progressing to duodenal cancer. This usually occurs later in life.
- Gastric fundic gland polyps are common, often florid, and harmless. Gastric adenomas and cancers can occur, but are rare.
- Desmoids develop in 20% of people with FAP. These are very rare, locally invasive, non-metastasising fibrous tumours. Most arise within the abdomen or in the abdominal wall, and in most (but not all) cases, growth is self-limiting.
- There are a number of other features including: osteoma, sebaceous cyst, adrenal mass (mostly non-hyperfunctioning adrenal adenoma), dental anomaly, CHRPE (harmless retinal patchy pigmentation), and an increased risk of thyroid cancer and of hepatoblastoma in children.

Diagnosis

- Most affected individuals are identified as being at risk because they are from a family known to have FAP, and are offered predictive genetic testing, usually between the ages of 12 and 14.
- Some patients present with symptoms caused by numerous large polyps or colorectal cancer, and are first diagnosed with FAP when colonoscopy is performed.
- In about 10% of individuals with over 100 large bowel adenomas, no alteration can currently be identified in *APC* or the other genes known to be associated with adenomatous polyposis.
- People with over 100 adenomas that have no established genetic cause should be managed as though diagnosed with FAP.

Genetic basis and genetic testing

- FAP is caused by variants in the *APC* gene.

- The *APC* gene codes for a complex protein with multiple functions, including formation of three-dimensional structures and the mitotic spindle.
- In the majority of cases, the pathogenic variant is inherited from a parent, but in 20% of cases, the variant has occurred 'de novo', or for the first time in an individual presenting with FAP.
- There is considerable genotype-phenotype correlation, with the clinical manifestations often being related to the site of the genetic variant within the *APC* gene.

Clinical management

- Prophylactic surgery to remove the colon (or in more severe cases, the colon and rectum) makes a dramatic difference to life expectancy, and is the cornerstone of management.
- Once the diagnosis is confirmed, a colonoscopy is needed to assess polyp number and size, to guide the timing and type of surgery.
- Prophylactic surgery is usually performed in the late teens, but can be delayed in some individuals with fewer, smaller polyps. Such individuals need regular (usually annual) colonoscopy.
- After surgery, any remaining large bowel, or ileoanal pouch reconstruction, requires regular endoscopic surveillance and removal of polyps as they enlarge. Sometimes further surgery is required if polyps become too large or numerous to be controlled endoscopically.
- Upper GI endoscopic surveillance is started when the patient is 25 years old, and repeated at intervals determined by adenoma burden.
- There is no evidence to support surveillance for desmoids, or of the thyroid, adrenals or liver in children.
- There have been trials of various chemoprevention agents in FAP, but none has been shown to reduce cancer risk, and their use is controversial.
- Pre-implantation genetic diagnosis is available for patients with FAP if they wish to have a child without the condition. Prenatal diagnosis (CVS/amniocentesis) can also be performed.

Direction to further reading, guidelines and patient groups

- There are a number of published guidelines on the management of FAP, including:
  - Guidelines for the clinical management of familial adenomatous polyposis (FAP). Vasen HFA, Möslein G, Alonso A, Aretz S, et al. Gut 2008;57:704–13.
  - Management of familial adenomatous polyposis in children and adolescents: position paper from the ESPGHAN Polyposis Working Group. J Pediatr Gastroenterol Nutr 2019;68:428–41.
  - Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Monahan KJ, Bradshaw N, Dolwani S Hereditary CRC guidelines eDelphi consensus group, et al. Gut 2020;69:411-444.
- Patient support group - www.polypeople.online
- St Mark's Hospital polyposis registry - www.polyposisregistry.org.uk

This information is intended for educational use and was current in June 2019. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and The Polyposis Registry, St Mark's Hospital.