Polymerase proofreading-associated polyposis

Key facts

- Polymerase proofreading-associated (PPAP) is a dominantly inherited disorder, resulting in a high risk of colorectal cancer and increased risk of other cancers.
- PPAP is caused by a variants of one of the two DNA polymerase proofreading genes: *POLE* and *POLD1*.
- This is a very rare condition, and has only been identified within the last 10 years, so clinical characterisation is incomplete and ongoing.

Clinical features

- Patients identified to date have multiple large bowel adenomas and early onset colorectal cancer (with a median age of 45 years). The risk of cancer may be lower with POLD1 variants (about 30% by 70 years of age) than with POLE variants (about 80% by 70 years of age).
- There is a significantly increased risk of endometrial cancer in women with a pathogenic variant in *POLD1*.
- Other cancers likely to be associated with the condition include breast, duodenal, ovarian and central nervous system.

Diagnosis

- Patients are diagnosed during the investigation of numerous large bowel polyps or early onset colorectal cancer, and are found to have PPAP on genetic testing.
- Individuals may be identified as being at risk because they are from a family known to have PPAP, and so are offered predictive genetic testing.

Genetic basis

- PPAP is caused by a variants of one of the two DNA polymerase proofreading genes: *POLE* and *POLD1*. These genes code for proteins involved in DNA repair, and loss of function results in the accumulation of multiple DNA mutations.
- Inheritance is dominant, with high penetrance.

Clinical management

- Colonoscopy should be started between the age of 18 and 20 years, and repeated according to polyp burden.
- Through the endoscopic removal of polpys, many patients can be managed for many years, or even indefinitely.
- If adenomas become endoscopically unmanageable, surgery (removal of the colon, and occasionally the rectum as well) is required.
- After surgery, any remaining large bowel or ileoanal pouch reconstruction requires regular endoscopic surveillance, and removal of polyps as they enlarge.

- Regular upper GI endoscopy should start at around 30 years of age.
- Currently, there is no evidence to support screening of other organs, but a high index of suspicion should be maintained if any symptoms develop.

Direction to further reading, guidelines and patient groups

- 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
- St Mark's Hospital Polyposis Registry

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 The Polyposis Registry, St Mark's Hospital.