Polyposis syndromes

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Polyposis syndromes can be divided into familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), MUTYH -associated polyposis (MAP) and NTHL1 associated polyposis (NAP). Eldon John Gardner , 1909–1989, geneticist, The University of Utah, Salt Lake City , UT , USA, described this syndrome in 1950. FAP is defined clinically by the presence of more than 100 colorectal adenomas but is also characterised by duodenal adenomas and multiple extraintestinal manifestations (Summary boxes 77.1 and 77.2). Over 80% of cases come from those with a positive family history . The remainder arise as a result of new mutations in the adenomatous polyposis coli (APC) gene on the long arm of chromosome 5. FAP is inher - ited as an autosomal dominant condition and is consequently equally likely in men and women. The lifetime risk of colorectal cancer is up to 100% in those with an APC gene mutation. FAP can also be associated with benign mesodermal tumours such as desmoid tumours and osteomas. Epidermoid cysts can also occur (Gardner’s syndrome); desmoid tumours in the abdomen spread locally to involve the intestinal mesentery and, although non-metastasising, they may become unresectable. Up to 50% of people with FAP have congenital hypertrophy of the retinal pigment epithelium (CHRPE), which can be used to screen a ff ected families if genetic testing is unavailable. Clinical features Polyps are usually visible on sigmoidoscopy by the age of 15 years and will almost always be visible by the age of 30 years. Regular endoscopic surveillance in a suspected family member should therefore commence at the age of 12–14 years, even if a genetic mutation has not been identified. Patients with mutations located between codons 1286 and 1513 of the APC gene generally have a worse prognosis with earlier disease onset than those with mutations outside this region. Germline mutations at codon 1309 are associated with the most severe disease. AFAP , also associated with APC gene mutation, is associated with fewer than 100 polyps and may not present until the fourth decade. If the diagnosis is made during adolescence, surgery is usu - ally deferred to the age of 17 or 18 years unless symptoms develop. Malignant change is unusual before the age of 20 years. Examination of blood relatives, including cousins , neph - ews and nieces, is essential; a family tree should be constructed, - and a register of a ff ected families maintained. Referral to a medical geneticist is essential. If over 100 adenomas are pres - ent at colonoscopy , the diagnosis can be made confidently (Figure 77.3). Summary box 77.1 Features of FAP /uni25CF /uni25CF /uni25CF /uni25CF -

Autosomal dominant inherited disease due to mutations of the APC gene More than 100 colonic adenomas are diagnostic Prophylactic surgery is indicated to prevent colorectal cancer Polyps and malignant tumours can develop particularly around the duodenal ampulla

Summary box 77.2 Extracolonic manifestations of FAP /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Treatment The aim of surgery in FAP is to prevent the development of colorectal cancer. The surgical options are: 1 restorative proctocolectomy with an ileal pouch–anal anastomosis; 2 colectomy with ileorectal

anastomosis (IRA); 3 total proctocolectomy and end-ileostomy . As patients are often young, most prefer to avoid a stoma, restorative proctocolectomy with ileal pouch–anal anastomosis has the advantage of removing the whole colon and rectum without the need for a permanent stoma (see Chapter 75 However, there is a pouch failure rate of approximately 10%. In addition, and particularly when a stapled anastomosis has been created, endoscopic surveillance is still required as malig nant change can occur in the ‘rectal cu ff ’ (the small strip of rectal mucosa between the pouch and the dentate line). Some advocate complete mucosectomy of this residual cu ff and a tion. In experienced hands, a laparoscopic approach is asso - ciated with swifter recovery , improved cosmesis and perhaps increased fecundity in women. For patients with relative rectal sparing (<20 polyps), total colectomy and IRA is an option to be considered, particularly as it is associated with less risk of sexual dysfunction in males and less infertility in females. Howe ver, the rectum requires regular endoscopic surveillance as up to 10% of patients will develop invasive malignancy in the rectum. In AFAP , patients may consider rectal preservation surgery on the understanding that their cancer risk is lower (around 2%) but still present. Proctocolectomy and ileostomy is the recommended option for patients with poor anal sphincter function, those who have already developed a r ectal cancer or those who wish to have a definitive single-stage procedure. Postoperative surveillance Because of the ongoing cancer risk, regular lifelong endoscopic surveillance of the rectum/pouch is important with biopsy of the rectal cu ff unless mucosal proctectomy has been performed. Endoscopy is also carried out to detect upper gastrointestinal tumours, particularly around the duodenal ampulla (see Chapter 67). A side-viewing duodenoscope is required. Despite surveillance, life expectancy is reduced because of extracolonic cancers and complications of desmoid tumours. MUTYH-associated polyposis The appearances of MAP can be similar to FAP but it is inherited as an autosomal recessive phenotype and predisposes individuals to multiple colonic polyps. If an APC pathogenic variant is not identified in an individual with colonic polyposis, molecular genetic testing of MUTYH should be considered. There is an increased risk of colorectal cancer of between three- and sixfold depending on the particular MUTYH mutation. Colonoscopy should be performed every 2 years. Colectomy is required when the number and/or characteristics of the polyps do not allow complete endoscopic resection or malignancy is diagnosed. Surveillance for duodenal adenomas is recommended. NTHL1 tumour syndrome NTHL1 tumour syndrome is a rare autosomal recessive cause of colorectal polyposis and increased lifetime risk for colorectal cancer. Colorectal polyps can be adenomatous, hyperplastic or sessile serrated. Management is similar to MAP . Peutz–Jeghers and juvenile polyposis syndrome Peutz–Jeghers syndrome (PJS) is an autosomal dominant genetic disorder characterised by the development of benign hamartomas in the gastrointestinal tract along with hyperpig -). mented lesions on the lips and oral mucosa. The main clinical risks are small bowel intussusception in children and increased incidence of gastrointestinal malignancy in adult life (see - Chapter 74). Juvenile polyposis (JPS) is an autosomal dominant inher - ited condition that presents with hamartomatous polyps due to

Figure 77.3 Familial adenomatous polyposis showing hundreds of adenomatous polyps.
Endodermal derivatives Adenomas and carcinomas, particularly around the duodenal ampulla but also stomach, small intestine, thyroid and biliary tree Gastric fundic gland polyps Hepatoblastoma
Ectodermal derivatives Epidermoid cysts Pilomatrixoma Congenital hypertrophy of the retinal pigment epithelium (CHRPE) Brain tumours
Mesodermal derivatives Desmoid tumours Osteomas Dental problems

tion characteristic of PJS is not present. Lynch syndrome (hereditary non-polyposis colorectal cancer) Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer (HNPCC), is characterised by an increased risk of colorectal cancer and also cancers of the endometrium, ovary , stomach and small intestine, urinary tract, pancreas, prostate and kidney . It is an autosomal dominant condition caused by a mutation in one of four DNA mismatch repair genes (MLH1 , MSH2 , MSH6 and PMS2). These genes, when func tioning normally , code for mismatch repair (MMR) proteins, which repair sporadic mutations that occur in other genes. If faulty , mutations accumulate in other key genes, leading to characteristic repea t sequences of DNA, termed microsatellite instability (MSI), and acceleration of the adenoma–carcinoma sequence. Thus individuals with an MMR gene mutation tend to develop colorectal polyps at an early age (before the age of 50 years) that quickly become cancerous. Not everyone with a mutation develops cancer; the lifetime risk is 80%. Most cancers develop in the proximal colon. Females have a 30–50% lifetime risk of developing endometrial cancer. Diagnosis Lynch syndrome was historically diagnosed based on a family history of cancer and the clinical parameters set out in the Amsterdam (Summary box 77.3) and Bethesda criteria. Recent advances in immunohistochemistry allow for MMR proteins or MSI to be accurately identified in all colorectal tumours with subsequent genetic testing in patients and fami lies of those proven positive. Summary box 77.3 Amsterdam II criteria /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Because of the accelerated pathway from adenoma to cancer in Lynch syndrome those with a gene mutation should be o ff ered 2-yearly endoscopic surveillance from age 25 years (MLH1 and MSH2 carriers) or 35 years (MSH6 carriers). PMS2 carriers should be o ff ered 5-yearly screening beginning at age 35 years (see Further reading). For patients with pol yps that cannot be managed with endoscopic polypectomy or those who develop a cancer, an extended colectomy (MLH1 and MSH2 carriers) should be considered. The benefit of screening other areas of the gastrointestinal tract is unclear Henry Thompson Lynch , 1928–2019, physician and geneticist, Omaha, NE, USA, first presented his findings of a family with a strong history of colorectal cancer without polyposis in 1964. with the 2019 Manchester Consensus (see Further reading).

Three or more family members with a Lynch syndrome-related cancer (colorectal, endometrial, small bowel, ureter, renal pelvis), one of whom is a /f_i rst-degree relative of the other two Two or more successive affected generations At least one tumour diagnosed before the age of 50 years FAP excluded Tumours veri /f_i ed by pathological examination

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