Peutz-Jeghers syndrome

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Peutz-Jeghers syndrome (PJS, MIM 175200) is a disease of autosomal dominant inheritance that is characterised by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation. In addition to problems such as intussusception, PJS predisposes to cancers of several sites. The unusual combination of clinical features makes the identification of the defect underlying PJS particularly interesting. Recently, the PJS gene has been mapped to chromosome 19p13.3. (J Med Genet 1997;34:1007–1011)

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Clinical features

The cardinal feature of PJS is the characteristic hamartomatous polyp of the gastrointestinal tract (figs 1 and 2). Between 70 and 90% of patients have polyps in the small bowel, one half have colorectal polyps, and one quarter have polyps in the stomach. The number of polyps per patient is variable and poorly recorded, but many fewer than in familial adenomatous polyposis (FAP). PJS polyps (fig 1) tend to be large and pedunculated. Microscopically, they consist of a branched or "frond-like" framework, with a core of stromal tissue and smooth muscle, which is surrounded by epithelial tissue with a near normal appearance. The hamartomatous polyps can also occur outside the gastrointestinal tract. Reported sites include the nose, uterus, respiratory tract, urinary tract, and gallbladder.

PJS patients often present as surgical emergencies with complications of the polyps (fig 2), such as intussusception, small bowel obstruction, bleeding per rectum, and volvulus. Typically, these complications occur in the first decade of life, although a relatively small proportion of polyps causes complications and some patients may have no gastrointestinal problems until middle age, if at all. Symptoms attributed to the polyps are non-specific, the commonest being abdominal pain and mild distension.

Usually, characteristic pigmentation (fig 3) accompanies the polyps and this may be noticed before the polyps come to light. The pigmentation takes the form of florid freckling of one or more of the following sites: lips, buccal mucosa, vulva, fingers, and toes. The freckling develops during the first decade of life, but usually fades from the third decade onwards. In addition, some patients with PJS polyps appear never to have had pigmentation, despite frequent, detailed medical examinations. Conversely, a few patients apparently affected on the basis of pigmentation are never known to have PJS polyps (perhaps reflecting subclinical polyposis rather than true absence of disease). It should also be borne in mind that some subjects have multiple, dark lentigines as a normal variant.

A family history of PJS is present in the majority of cases, and a suggestive history (such as relatives who have died from gastrointestinal cancer) is present in many more. No study has analysed the family histories of a truly unselected set of PJS cases and it seems likely that there is under-reporting of cases without a clear family history. Family history can be useful in making a diagnosis of PJS, but requires careful use. It is possible to place too great a significance on non-specific symptoms such as recurrent abdominal pain, to misclassify normal variants such as heavy freckling, and even to assess wrongly the histology of gastrointestinal polyps when small or with architecture distorted by diathermy.

It is not clear whether all subjects with PJS polyps carry a germline PJS mutation. There is currently no reason to exclude the possibility that truly sporadic PJS hamartomas can develop, although such lesions are unlikely to be multiple or accompanied by pigmentation. About 10-20% of PJS cases present with multiple polyps and pigmentation and no known family history; the relative contributions of new mutations, low penetrance alleles, and imperfect histories to these cases are unknown, although the disease appears to have a

Figure 1 PJS polyp with benign, proliferating glandular tissue and smooth muscle core (H&E).
Operative removal of a hamartomatous polyp with a wide base.

Figure 2

Penetration of pigmentation following in polyp in history of made in can either freckling. There are no been tract, and ovary, and associated cancers and gastrointestinal melaminous polyp our gastro intestinal melanin reports the PJS. Presumptive diagnoses the a (1) on (2) in pigmentation of the index finger.  

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Figure 3 Melanin pigmentation in PJS. (A) Symmetrical distribution of pigmentation on the lips and perioral region. (B) Pigmentation on the index finger.

Cancer risk

There are several published reports of PJS associated with cancers of the gastrointestinal tract, pancreas, breast (sometimes bilateral), ovary, and gallbladder. Before 1963, there had been no reports of deaths from gastrointestinal cancers and the prevailing belief was that the hamartomatous polyps had little or no malignant potential since there were no deaths from metastatic cancers in any of the early reports. A reversal of this belief came with the demonstration of dysplasia and carcinoma in situ within biopsied polyps and from the systematic follow up of PJS patients. Table 1 details the cancers reported in association with PJS from four large follow up studies and two studies of single large families.

The study reported by Giardiello et al was based on a 13 year follow up of 31 PJS patients from 13 unrelated families. Cancer developed in 15 patients. The majority of cancers arose at sites outside the gastrointestinal tract (pancreas, lung, uterus, and ovary). None of the patients followed up developed small bowel malignancies. The relative risk of cancer at all sites was 18 and the relative risk of pancreatic cancer was 100.

Linos et al reviewed 48 patients with PJS who had been followed up for a median period of 33 years. The risks of cancer were strongly dependent upon the criteria used to diagnose PJS. Of 21 patients in whom the syndrome could be unequivocally defined, cancer developed in six. Of 15 patients in whom the diagnosis was based solely on mucocutaneous pigmentation, one woman developed breast cancer. Of seven patients in whom the diagnosis was based upon mucocutaneous pigmentation and adenomatous or hyperplastic polyps, carcinoma developed in three. In the five patients who had hamartomatous polyps but no evidence of mucocutaneous pigmentation, none developed cancer. Overall survival was similar to the general population. If, however, the analysis was restricted to those in whom the diagnosis was unequivocally made, the cancer risks were comparable to those of Giardiello et al.

Seventeen of the 72 PJS patients followed up by Spigelman et al developed cancer. Ten of these cancers originated within the gastrointestinal tract. The relative risk of death from gastrointestinal cancer was estimated to be 13 (95% CI 2.7-38.1) and the relative risk of non-gastrointestinal cancer was 9 (95% CI 4.2-17.3). By the age of 57, the chance of dying of cancer was 48% and the chance of dying from all causes was 57%.

One of the largest systematic studies of the natural history of PJS patients was reported by Utsunomiya et al and consisted of a follow up of 102 patients. Of 36 follow up patients who died, 17 had developed cancer, 12 of which were in the gastrointestinal tract. The mortality by the age of 60 in PJS patients was estimated to be 38.5%.

One of the families first reported by Peutz was the subject of a 49 year follow up study reported by Foley et al. Of the 12 subjects in the family who had PJS, two were diagnosed with cancer. A similar long term follow up (27 years) of a single Peutz-Jeghers family was made by Burdick and Prior. Of the 10 affected family members, two developed breast cancer, one a jejunal carcinoma, and one a sex cord tumour of the ovary. The increased risk of cancer in these two families is similar to the cancer
risk in 13 families ascertained by our colleagues and us (17 subjects with 21 cancers out of a total of 48 affected with PJS).

There have been over 30 reports of an association between PJS and the rare sex cord tumour with annular tubules (SCTAT). SCTAT is a distinctive ovarian neoplasm in which the predominant component has morphological features intermediate between the granulosa cell tumour and the Sertoli cell tumour. Focal differentiation into either granulosa cell or Sertoli cell tumours may occur. In association with PJS, SCTAT is typically multifocal, bilateral, very small or microscopic, and calcified. Most are incidental findings, raising the possibility that they may almost be a pathognomonic feature of PJS. SCTAT produces clinical symptoms owing to hyperoestrogenism, menstrual irregularity, postmenopausal bleeding, and precocious puberty. In association with PJS, these tumours are generally benign, although at least one malignant SCTAT has been reported. The high oestrogen levels can lead to the development of adenoma malignum of the cervix. In a survey of 27 cases of SCTAT associated with PJS reported by Young et al., 12 patients had symptoms indicative of hyperoestrogenism and four patients developed adenoma malignum, leading to death in two. Testicular tumours with features of SCTAT have also been described in association with PJS but are rare compared with the frequency in females. In the cases reported, the hyperoestrogenism led to feminisation.

Some reports of small bowel cancers in PJS patients may be attributable to overdiagnosis of malignancy in polyps. Owing to the unusual histological features of the disorder, islands of epithelial cells may be seen in the submucosa or muscular layers of the bowel wall and can be mistaken for infiltration or distant metastasis. However, the development of cancer at sites outside the gastrointestinal tract cannot be open to question on this basis. It is impossible to exclude selection in the recruitment to these studies. However, it is very unlikely that bias could account for the high frequency of cancers observed, the young age at diagnosis, and the number of different sites involved. These factors strongly support the notion that PJS confers an increased risk of cancer.

Differential diagnosis
The combination of hamartomatous polyps and typical pigmentation should allow PJS to be diagnosed without problem in most cases. Occasionally, however, there is difficulty distinguishing it from: (1) juvenile polyposis (MIM 174900); no pigmentation, hamartomas of different histology; (2) hereditary mixed polyposis (MIM 601228); no pigmentation, coexisting adenomas; and (3) syndromes of metastasising such as Leopard syndrome (MIM 151100) none with the same pattern, none with polyps.

The underlying defect in PJS
The nature of the defect in PJS has been the subject of much speculation. The freckling is said to result from a failure to transfer melanin from melanocytes to keratinocytes, but there is little evidence for this hypothesis. Classically, hamartomas are not thought to be clonal, neoplastic lesions, but this is largely a morphological diagnosis with little molecular evidence in support. At the moment, no hypothesis can be excluded: the defect may lie in cell adhesion, proliferation, programmed cell death, cell-cell communication, or any other process with a credible role in maintaining the integrity of the epithelium.

Genetics
PJS has a relatively clear cut phenotype, but attempts to map the PJS locus have taken somewhat longer than expected owing to the rarity of the disease, its perceived lack of
importance before the risks of cancer became apparent, its frequently poor prognosis and hence moderate sized families, and the likelihood of genetic heterogeneity. This last possibility derived from the suggestion that failure of cell-cell interaction underlies the disease, so that mutations at a ligand or receptor locus could result in PJS.16

Markie et al22 reported a pericentric inversion of chromosome 6 in a patient with PJS. Linkage studies found no evidence that the long arm breakpoint was the site of a PJS locus. A set of families from the UK and Japan was linked to the short arm breakpoint (MLS -4.30), but there was no evidence of linkage in a number of French families.16 The possibility of genetic heterogeneity thus existed, with one locus close to the chromosome 6cen.

Published abstracts suggested the site of an additional or alternative PJS locus on chromosome 1p32-p34 (MLS (multipoint) -4.0) from a study of pedigrees.17 This is close to the hypothesised site of a modifier of FAP. Subsequent extension of the pedigrees did not, however, confirm the original linkage (C Amos, personal communication) and no evidence was found for linkage to 1p32-p34 in a different set of families.18 The problems with linkage analysis were circumvented by the use of comparative genomic hybridisation (CGH) in multiple polyps from a single PJS patient. The use of CGH relied on the assumptions (1) that the PJS locus is a tumour suppressor gene, (2) that the wild type allele would be deleted in the polyps, (3) that the hamartomas actually contain some tissue that is a clonal neoplasm, and (4) that the amount of stromal tissue in the polyps would not obscure deletions in any neoplastic component. Despite these potential problems, CGH detected deletions at the short arm telomere of chromosome 19 in a study of 10 PJS polyps. Subsequent linkage analysis found a MLS (multipoint) of 7.00 at marker D19S886, with no evidence of genetic heterogeneity, using a set of 18 families of diverse ethnic origins.

Management and screening

Acute medical problems and cancers in PJS patients do not require any significantly different treatment from sporadic cases. The aim of screening is to minimise the risk of these complications. Screening is necessarily based on theoretical considerations, rather than on data as to its efficacy. The emphasis of screening should alter from prevention of intussusception and bowel obstruction in children to prevention of cancer in adults.

Patients with PJS should be screened for gastrointestinal polyps and cancers of the breast, ovary, and uterus. The following protocol is suggested: (1) two yearly upper gastrointestinal endoscopy from the age of 10 (or less, if clinically indicated) with frequency titrated to patient’s history; any polyp larger than 1 mm should be removed; (2) three yearly colonoscopy from the age of 25, with frequency titrated to patient’s history; all polyps larger than 1 mm should be removed; (3) small bowel follow through screening from the age of 10 (or less, if clinically indicated); small bowel screening presents particular problems; a standard frequency of two yearly follow through contrast imaging has been suggested, but this time interval should be lengthened whenever possible on the basis of clinical history to minimise radiation exposure; (4) breast surveillance from the age of 25 and annual mammography from the age of 35; (5) annual abdominal and pelvic ultrasound (for ovarian and uterine cancers) from the age of 25; and (6) two yearly cervical smear tests as part of the population screening programme.

Epileptiform surgery should be performed to remove any polyp greater than 1 cm in size that cannot be removed by endoscopy, and on-table enteroscopy can be performed at this time.

The screening of at risk members of PJS families is more controversial, given the uncertain age dependence of disease penetrance. Linkage analysis can be used to identify non-carriers in larger families that are clearly linked to 19p13.3. Those with clear cut PJS pigmentation (or those who have inherited a mutant PJS allele in a 19p13.3 linked family) should be entered into the above screening programme. Those with absent or sparse PJS type freckling cannot be classed as unaffected (unless they have inherited a normal PJS allele in a 19p13.3 linked family). We suggest that these people should have diagnostic investigation and then a low level of screening. If, however, the subject has developed neither polyps nor typical pigmentation by the age of 30, it is probably unnecessary to continue screening.

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6 Sommerhaug RG, Mason T. Peutz-Jeghers syndrome and uterine polypsis. JAMA 1970;211:112-0.