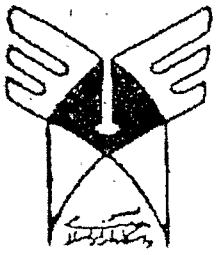

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Subject:
Prevalence rate of complications in patients with Peutz-Jeghers syndrome in training centers of hospitals in Tehran

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LIST

Prevalence rate of complications in patients with Peutz-Jeghers syndrome in training centers of hospitals in Tehran

Current survey was a descriptive cross-sectional study among 38 patients with Peutz-Jeghers syndrome. Mean age of them was 23.79 with standard deviation of 9.06 years. 52.6% were male and 47.4% were female. 65.8% had positive familial history of Peutz-Jeghers syndrome. 32 patients (84.2%) developed complications which were mostly (62.5%) from gastrointestinal types. Positive familial history significantly increased the rate of complications (P=0.001).

Keywords: **Peutz-Jeghers syndrome, Complications**

INTRODUCTION

Introduction

Peutz-Jeghers syndrome is an autosomal dominant inherited disorder characterized by intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules. Although the intestinal lesions are hamartomas, patients with Peutz-Jeghers syndrome have a 15-fold increased risk of developing intestinal cancer compared to that of the general population. Cancer location includes gastrointestinal and extraintestinal sites. The syndrome was described in 1921 by Peutz, who noted a relationship between the intestinal polyps and the mucocutaneous macules in a Dutch family. Subsequently, Jeghers is credited with the definitive descriptive reports in the 1940s.

The gastrointestinal polyps found in Peutz-Jeghers syndrome are typical hamartomas. Their histology is characterized by extensive smooth muscle arborization throughout the polyp. This may give the lesion the appearance of pseudoinvasion, because some of the epithelial cells, usually from benign glands, are surrounded by the smooth muscle. Nevertheless, cancer may develop in the gastrointestinal tract of patients

with Peutz-Jeghers syndrome with a higher frequency than in the general population. Also because of low prevalence of this syndrome, it may be missed and patients would attend with complications of disease. Therefore and because of issue importance, we performed current study to determine the prevalence rate of complications in patients with Peutz-Jeghers syndrome in training centers of hospitals in Tehran.

REVIEW OF LITERATURES

Review of Literatures

Pathophysiology: The cause of Peutz-Jeghers syndrome appears to be a germline mutation of the *STK11/LKB1* (serine/threonine kinase 11) gene in most cases, located on band 19p13.3. Penetrance of the gene is variable, causing varied phenotypic manifestations among patients with Peutz-Jeghers syndrome (eg, inconsistent number of polyps, differing presentation of the macules) and allowing for a variable presentation of cancer.

Because the signaling pathway of the *STK11* gene product currently is not identified, the mechanism of hamartomatous polyp formation and mucocutaneous pigmentation is not known. In cancer formation, *STK11* inactivation appears to occur early and might be followed by interruption of the APC/β-catenin and p53 pathways, but this has not been fully elucidated. However, the cyclic adenosine monophosphate (cAMP)–dependent protein kinase A apparently can phosphorylate the murine STK11 protein in vitro; the significance of this currently is not known, but this phosphorylation may be important for STK11 regulation. *STK11*

may be a tumor suppressor gene in that its overexpression can induce a growth arrest of a cell at the G1 phase of the cell cycle and that somatic inactivation of the unaffected allele of *STK11* often is observed in polyps and cancers from patients with Peutz-Jeghers syndrome.

STK11/LKB1 seems to regulate both cell polarity and tumor suppression, predisposing patients to mucosal prolapse first, leading to polypoid lesions and at the same time cancer.

Frequency:

- **In the US:** Peutz-Jeghers syndrome is rare, with a frequency of encounter from polyposis registries one tenth that of familial adenomatous polyposis. This would place the frequency from 1 case per 60,000 people to 1 case per 300,000 people.
- **Internationally:** International frequency is unknown.

Mortality/Morbidity:

- The principal causes of morbidity in Peutz-Jeghers syndrome stem from the intestinal location of the polyps (ie, small intestine, colon, stomach). Morbidity includes small intestinal obstruction and

intussusception (43%), abdominal pain (23%), hematochezia (14%), and prolapse of a colonic polyp (7%), and these typically occur in the second and third decades of life.

- Almost 50% of patients with Peutz-Jeghers syndrome develop and die from cancer by age 57 years. The mean age at first diagnosis of cancer is 42.9 years, add or subtract 10.2 years. The cumulative risk for developing any cancers associated with Peutz-Jeghers syndrome in patients aged 15–64 years is 93%. The cumulative risks of developing a particular cancer from ages 15-64 years are as follows: esophagus 0.5%, stomach 29%, small intestine 13%, colon 39%, pancreas 36%, lung 15%, testes 9%, breast 54%, uterus 9%, ovary 21%, and cervix 10%.
- In a meta-analysis of 210 patients with Peutz-Jeghers syndrome, the following organ sites had a statistically significant elevated relative risk (RR) for cancer formation over the general population (with confidence intervals [CI]): all cancers (RR 15.2, CI 12-19), esophagus (RR 57, CI 2.5-557), stomach (RR 96, CI 96-368), small

intestine (RR 520, CI 220-1306), colon (RR 84, CI 47-137), pancreas (RR 132, CI 44-261), lung (RR 17, CI 5.4-39), breast (RR 15.2, CI 7.6-27), uterus (RR 16.0, CI 1.9-56), and ovary (RR 27, CI 7.3-68).

- Intestinal obstruction can occur in about 50% of patients and is usually localized in the small bowel. Obstruction can be complete or incomplete and is caused by the polyp itself or by the subsequent intussusception that may occur.

Race: Peutz-Jeghers syndrome has been described in all races. Peutz described the syndrome in a Dutch family in 1921.

Sex: The occurrence of cases in males and females is about equal.

Age: The average age at diagnosis is 23 years in men and 26 years in women. Pigmented lesions are present in the first years of life and may fade at puberty, except for those on the buccal mucosa, making diagnosis possible in pediatric patients with a high level of suspicion.

CLINICAL

History: Peutz-Jeghers syndrome is characterized by the combination of pigmented lesions in the buccal mucosa and gastrointestinal polyps. The number, as well as the size and the location, of polyps may vary from patient to patient. Isolated melanotic mucocutaneous pigmentation without gastrointestinal polyps has also been described because of the genetic variability of the syndrome. The risk of cancer remains elevated with disregard to the presence or the absence, as well as the number, of gastrointestinal polyps.

- Family history of Peutz-Jeghers syndrome
- Repeated bouts of abdominal pain in patients younger than 25 years
- Unexplained intestinal bleeding in a young patient
- Prolapse of tissue from the rectum
- Menstrual irregularities in females (due to hyperestrogenism from sex cord tumors with annular tubules)

- Gynecomastia in males (possible due to the production of estrogens from Sertoli cell testicular tumors)
- Precocious puberty
- Gastrointestinal intussusception with bowel obstruction

Physical: Mucocutaneous pigmentation and melanin spots are typical of patients with Peutz-Jeghers syndrome and are present in more than 95% of cases. They appear as small, flat, brown or dark blue spots with an appearance of freckles, most commonly in the peribuccal area.

- Cutaneous pigmentation (1- to 5-mm macules) is usually located in the perioral region, crossing the vermilion border (94%), in the perinasal and perioral areas.
    - They may be present on the fingers and the toes, on the dorsal and volar aspects of the hands and the feet (62-74%), and around the anus and genitalia.
    - They may fade after puberty.
- Mucous membrane pigmentation, primarily the buccal mucosa (66%) and rarely the intestinal mucosa

- Localization in the oral mucosa is typical of patients with Peutz-Jeghers syndrome and does not happen with other types of dermatologic pigmented lesions, such as common lentigo. Freckles do not localize in the buccal mucosa.
- A rectal mass (rectal polyp) may be found during a rectal examination. In rare cases (7% of cases), the polyp can prolapse outside the anus if it reaches a significant size.
- Gynecomastia and growth acceleration (due to Sertoli cell tumor)
- Testicular mass

Causes: The cause of Peutz-Jeghers syndrome appears to be a germline mutation of the *STK11* gene, located on band 19p13.3. This protein is likely regulated by phosphorylation by cAMP-dependent protein kinase A.

DIFFERENTIALS

Familial Adenomatous Polyposis

Other Problems to be Considered:

Bannayan-Riley-Ruvalcaba syndrome

Cowden disease

Cronkhite-Canada syndrome

Gardner variant of familial adenomatous polyposis

Juvenile polyposis syndrome

WORKUP

Lab Studies:

- The polyps may ulcerate and be a source of blood loss and anemia. Gastrointestinal bleeding may be massive but also microscopic with subsequent iron deficiency. Cell counts and iron studies should be monitored.
- The carcinoembryonic antigen (CEA) test has been used by some physicians for screening and monitoring of cancer degeneration.
- Hemoccult, a type of fecal occult blood test (FOBT), should be performed to check for blood in the stool.

Imaging Studies:

- Enteroclysis study (preferred) and dedicated small bowel follow-through x-rays are used to determine the presence and the location of small intestinal polyps.

- Esophagogastroduodenoscopy
- Colonoscopy
- Capsule enteroscopy
- Push enteroscopy, intraoperative enteroscopy, and double-balloon enteroscopy (diagnostic and therapeutic options)
- Imaging studies of the liver and the pancreas are indicated because of the risk of pancreatic cancer as well as of gallbladder polyps and cancer. These imaging studies may include ultrasonography as well as CT with pancreatic details or magnetic resonance cholangiopancreatography (MRCP).

Procedures:

- Hemorrhagic or large polyps (>5 mm) should be removed by endoscopic polypectomy to confirm the diagnosis and help control symptoms.
- Laparotomy and resection should be performed for repeated or persistent small intestinal intussusception, obstruction, or persistent intestinal bleeding.

Histologic Findings: Characteristic histology of Peutz-Jeghers polyps includes extensive smooth muscle arborization throughout the polyp, with the appearance of pseudoinvasion because some of the epithelial cells, usually from benign glands, are surrounded by the smooth muscle.

TREATMENT

Medical Care: Peutz-Jeghers syndrome should be promptly diagnosed in patients as early as possible. Genetic counseling should also be provided. Many of the gastrointestinal lesions will start developing early in life even if the syndrome is clinically apparent in the second and third decades of life. Proper screening for both intestinal cancers and extraintestinal cancers should be implemented.

- Annual physical examination that includes evaluation of the breasts, abdomen, pelvis, and testes
- Annual complete blood count
- Removal of hemorrhagic or large polyps (>5 mm) by endoscopic polypectomy
- Some suggestions for surveillance for cancer include the following:

- Small intestine with small bowel radiography every 2 years
- Esophagogastroduodenoscopy and colonoscopy every 2 years
- Ultrasound of the pancreas yearly
- Ultrasound of the pelvis (women) and testes (men) yearly
- Mammography (women) at ages 25, 30, 35, and 38 years, then every 2 years until age 50 years, then annually
- Papanicolaou (Pap) test every year

Surgical Care: Patients with Peutz-Jeghers syndrome usually undergo numerous surgeries during their lives. These surgeries include laparotomies and laparoscopies for both gastrointestinal problems and extraintestinal problems.

- Push enteroscopy and interoperative enteroscopy with polypectomy are used to remove larger polyps and may defer the need for repeated small bowel resections.

- Laparotomy and resection, as indicated, for small intestinal intussusception, obstruction, or persistent intestinal bleeding may be necessary.
- Surgical treatment of extraintestinal cancers detected by surveillance and diagnosis is required.

Consultations:

- Follow-up care should be supervised by a gastroenterologist familiar with Peutz-Jeghers syndrome.
- Genetic consultation and counseling as well as urological and gynecological consultations are required in the management of these patients.

Activity: No activity restraints should be made.

FOLLOW-UP

Complications:

- In young patients, small intestinal obstruction and intussusception are the main complications of Peutz-Jeghers syndrome. This is due to the small intestinal location of the polyps.