Peutz Jeghers Syndrome

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Synonyms of Peutz Jeghers Syndrome

- PJS
- polyposis, hamartomatous intestinal
- polyps and spots syndrome

General Discussion

Summary

Peutz Jeghers syndrome (PJS) is an autosomal dominant genetic condition affecting around 1/50,000 and 1/200,000 individuals. Symptoms usually appear during the first decade of life and begin with spots of dark skin freckling (melanocytic macules) around the mouth, eyes, nostrils, fingers as well as inside the mouth (oral mucosa) and around the anus (perianal). Multiple benign polyps called hamartomas also begin to grow in the gastrointestinal tract of affected individuals around that age. These polyps are located throughout the gastrointestinal tract and can cause nausea, vomiting, abdominal pain, intestinal obstruction and rectal bleeding. Abdominal surgery or endoscopic procedures might be necessary to remove polyps (polypectomy) to prevent polyps-related complications, such as folding of the intestine into itself (intussusception). Affected individuals have an increased risk for intestinal and other cancers. Frequent medical examination and testing is necessary to allow early detection of polyps and cancer.

Introduction

Peutz Jeghers syndrome is part of a heterogeneous group of disorders, known as hamartomatous polyposis syndromes that involve the growth of multiple polyps in the gastrointestinal tract of affected individuals. It was first described in a pair of twin sisters with dark pigment spots on their lips and oral mucosa by Dr. J.T. Connor in 1895. These symptoms were attributed to a familial syndrome in 1921, when Dr. Jan Peutz described four affected siblings. The syndrome was then defined as a distinct entity by Dr. Harold Jeghers in 1949 when he described 10 cases and was subsequently named Peutz

Jeghers syndrome in 1954 by Dr. Andre Bruwer. The gene causing PJS (*STK-11/LKB1*) was identified in 1998 and allows early detection of the disease and screening of family members.

Signs & Symptoms

PJS is characterized by the growth of multiple benign polyps called hamartomas on the mucous lining of the gastrointestinal system and spots of dark blue to dark brown skin freckling (melanocytic macules) around the mouth, eyes, nostrils, fingers, oral mucosa and anus (perianal). These melanocytic macules can appear as early as the first year of life and are present in most affected children under five years of age. They tend to fade away with age and might completely disappear in puberty or adulthood, although they tend to persist in the oral mucosa. Polyps also begin to grow within the first years of life, but associated symptoms typically arise between 10 to 30 years of age. Around half of patients with PJS have to undergo surgery by age 18 because of polyps-related complication. Polyps most often tend to develop in the small intestine (in the jejunum, specifically) but can also arise in the stomach and large intestine. Rarely, polyps can grow outside the gastrointestinal tract and affect the ureters, bladder, lungs, bronchi, and gallbladder. Gastrointestinal polyps can cause abdominal pain, vomiting, diarrhea, intestinal obstruction and rectal bleeding, which can lead to anemia. They can also provoke folding of the intestine into itself (intussusception), which can lead to severe abdominal pain and emergency surgery.

Individuals with Peutz Jeghers syndrome are at a highly increased risk of developing gastrointestinal and other cancers including breast, cervical, uterine, pancreas, and lung. The lifetime risk of developing cancer in affected individuals can be as high as 93%. Individuals that develop cancer are usually affected around their fifth decade of life (age 40-49). Affected females have an increased risk for a benign ovarian tumor called SCTAT (sex cord tumors with annular tumors) for which symptoms may include irregular or heavy periods or early puberty. Usually before age 20, affected males can develop a tumor in the testes, called Sertoli cells carcinoma that secretes estrogen and can lead to breast development (gynecomastia).

Causes

Peutz Jeghers syndrome is an autosomal dominant genetic condition caused by mutations in the *STK11/LKB1* gene. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent, or can be the result of a new mutation (*de novo*) in the affected individual. The risk of passing the abnormal gene from an affected parent to an offspring is 50% for each pregnancy. The risk is the same for males and females.

Approximately 60-78% of individuals with PJS have an affected relative. Around 80-94% of PJS patients have an identified mutation in the *STK11* gene, which means that other genes are possibly involved in the disease. More than 200 disease-causing (pathogenic)

mutations have been reported and the penetrance of these mutations is thought to be 100%, meaning that an individual carrying a pathogenic mutation will necessarily develop the disease.

The *STK11* gene produces a protein that is involved in the regulation of cell division and programmed cell death (apoptosis). It also interacts with p53, a major tumor suppression protein. Pathogenic mutations in *STK11* lead to either cessation or dysfunction of protein production by the gene and uncontrolled cell growth, which can in turn lead to the development of benign polyps (hamartomas) and cancer.

The dark pigmented spots (melanocytic macules) are thought to be caused by inflammation and blockage of melanin migration from cells where it is produced (melanocytes) to cells forming the outermost layer of the skin (keratinocytes).

Affected Populations

Peutz Jeghers syndrome is a rare disorder that affects males and females in equal numbers and can occur in any racial or ethnic group. The birth prevalence of PJS is estimated to be between 1/50,000 and 1/200,000. Limited evidence shows that the disease might be more prevalent in certain countries such as the Netherlands and China. Women are at a higher risk of developing cancer compared to men, as PJS increases the likelihood of developing breast, ovarian, cervical, and uterine cancer.

Related Disorders

Symptoms of the following disorders can be similar to those of Peutz-Jeghers syndrome. Comparisons may be useful for a differential diagnosis:

Juvenile polyposis syndrome is an autosomal dominant genetic disorder characterized by a specific type of hamartomatous polyp referred to as a juvenile polyp . Most polyps are benign but affected individuals are at an increased risk for colon and other cancers.

Serrated polyposis syndrome is an autosomal dominant genetic disorder characterized by a specific type of polyp referred to as a serrated (saw-tooth) polyp located in the colorectum. Most polyps are benign but serrated polyposis is associated with an increased personal and family history of colorectal cancer.

Familial adenomatous polyposis (FAP) is a rare inherited cancer predisposition syndrome characterized by hundreds to thousands of precancerous colorectal polyps (adenomatous polyps). If left untreated, affected individuals inevitably develop cancer of the colon and/or rectum at a relatively young age. FAP is inherited in an autosomal dominant manner and caused by mutations in the *APC* gene. (For more information on this disorder, choose “familial adenomatous polyposis” as your search term in the Rare Disease Database.)

Turcot syndrome is a rare inherited disorder characterized by the association of benign growths (adenomatous polyps) in the mucous lining of the gastrointestinal tract with tumors of the central nervous system. Symptoms associated with polyp formation may

include diarrhea, bleeding from the end portion of the large intestine (rectum), fatigue, abdominal pain, and weight loss. Affected individuals may also experience neurological symptoms, depending upon the type, size and location of the associated brain tumor. Researchers believe that Turcot syndrome is a variant of familial adenomatous polyposis or Lynch syndrome (hereditary nonpolyposis colorectal cancer). (For more information on this disorder, choose “Turcot syndrome” as your search term in the Rare Disease Database.)

Hereditary mixed polyposis syndrome is an autosomal dominant genetic disorder characterized by the development of multiple types of polyps (atypical juvenile polyps, hyperplastic polyps, sessile serrated adenomas, and adenomatous polyps) in the gastrointestinal tract. Affected individuals are at an increased risk for colorectal cancer.

The PTEN hamartoma tumor syndrome (PHTS) is a spectrum of disorders caused by mutations in the *PTEN* tumor suppressor gene. These disorders are characterized by multiple hamartomas that can affect various areas of the body. Findings in PHTS also include increased risk for certain types of cancer and neurodevelopmental disorders. The symptoms of PHTS vary greatly from person to person and can develop at any age. (For more information on this disorder, choose “PTEN hamartoma tumor syndrome” as your search term in the Rare Disease Database.)

Cronkhite-Canada syndrome (CCS) is an extremely rare disease characterized by various intestinal polyps, loss of taste, hair loss, and nail growth problems. CCS occurs primarily in the older population (average age 59) and predominantly occurs in males. It is considered to be an acquired, not hereditary, disease. (For more information on this disorder, choose “Cronkhite-Canada syndrome” as your search term in the Rare Disease Database.)

Multiple endocrine neoplasia type 2 (MEN2) is a rare genetic disorder characterized by an increased risk of developing a specific form of thyroid cancer (medullary thyroid carcinoma) and benign tumors affecting additional glands of the endocrine system. Individuals with one particular type of the syndrome, called MEN2B, can develop benign growths arising from nerve cells called ganglion cells (ganglioneuromatosis). These growths occur in the gastrointestinal tract and may cause swelling (distention) of the abdomen, diarrhea, constipation, and an abnormally enlarged colon (megacolon). Affected infants often fail to gain weight and grow at the expected rate for age and sex (failure to thrive). (For more information on this disorder, choose “multiple endocrine neoplasia type 2” as your search term in the Rare Disease Database.)

Carney complex is a rare genetic disorder characterized by multiple benign tumors (multiple neoplasia) most often affecting the heart, skin and endocrine system and abnormalities in skin coloring (pigment) resulting in a spotty appearance to the skin of affected areas. Benign tumors of connective tissue (myxomas) are common in individuals with Carney complex and, most often, are found in the heart where they can potentially cause serious, life-threatening complications including stroke, valvular obstruction or heart failure. A wide variety of endocrine abnormalities potentially can occur in Carney complex affecting a variety of glands. Additional tumors include

myxomas affecting the skin and nerve sheath tumors (schwannomas). Skin pigment abnormalities include tiny flat (freckle-like) black or brown spots (multiple lentigines) and small, blue or bluish-black spots (blue nevi). (For more information on this disorder, choose “Carney complex” as your search term in the Rare Disease Database.)

Diagnosis

A clinical diagnosis of Peutz Jeghers syndrome can be made when any one of the following criteria is present:

- Presence of at least two PJS polyps
- Any number of PJS polyps and at least one close relative diagnosed with PJS Characteristic dark pigmented spots (melanocytic macules) and at least one close relative diagnosed with PJS
- Any number of PJS polyps and characteristic dark pigmented spots

The melanocytic macules can be identified with a physical examination. Polyps can be detected by endoscopy, x-ray examination, or wireless capsule endoscopy and are classified as PJS polyps by microscopic examination.

Genetic testing for the identification of disease-causing (pathogenic) mutations in the *STK11* gene is recommended when any one of the following criteria is present:

- Characteristic dark pigmented spots (melanocytic macules)
- Presence of at least two PJS polyps
- Family history of PJS

Genetic testing is particularly useful when a pathogenic mutation has already been identified in a family. The penetrance of the *STK11* gene mutation is thought to be 100% (which means that someone with a pathogenic mutation has a 100% chance of developing the disease), so genetic testing can give a definite diagnosis before symptoms appear. About half of PJS patients are diagnosed with genetic testing before the appearance of symptoms.

Standard Therapies

Treatment

A consultation with a clinical geneticist or genetic counselor should be offered. As there is no cure for Peutz Jeghers syndrome, treatment is mostly focused on surveillance and control of symptoms. After initial diagnosis, it is recommended that individuals older than 8 years or having symptoms undergo endoscopic and small bowel examination. The latter can be done with magnetic resonance imaging of the intestines (magnetic resonance enterography, MRE) or by swallowing a capsule that records internal images from inside the gastrointestinal tract (video capsule endoscopy, VCE). Gynecologic and breast examination are also recommended for women older than 18 years. Testicular examination is recommended for men.

Following initial workup after the diagnosis, endoscopy, colonoscopy, and small bowel examination should be performed every 2-3 years to detect polyps and potential tumors. An annual mammogram is recommended for women. Testicular ultrasound can be done every two years for men.

As PJS increases the risk of breast, uterine, and ovarian cancer, it is possible for affected women to undergo preventive mastectomy, hysterectomy or salpingo-oophorectomy (surgical removal of the breasts, uterus, and fallopian tubes and ovaries, respectively).

Polyps over 1 cm in size are removed with endoscopic techniques to avoid polyps-related complications such as bleeding and intussusception. These complications might require surgical interventions to be corrected. If a patient undergoes surgery, endoscopic removal of polyps (polypectomy) is performed at the same time as surgery to reduce the risk of recurrence of complications and surgery.

In cases where dark pigmented spots (melanocytic macules) have a greatly negative psychological impact on affected individuals, they can be partially removed with laser treatment.

Investigational Therapies

A few medications based on the molecular biology of PJS and testing in animal models have shown promise for prevention of polyps in PJS patients. However, human clinical trial data is very limited as of 2018.

Polyps present in Peutz Jeghers syndrome overexpress and enzyme called COX2. A drug called celecoxib, which is a COX2 inhibitor, has been showed to reduce the number of polyps in mice models of PJS and might be helpful in humans to reduce polyp burden.

STK11 (the gene involved in PJS) is normally producing a protein that is involved in the inhibition of mTOR, a protein promoting cellular growth and proliferation. mTOR inhibitors such as rapamycin and everolimus have successfully reduced polyp burden in mice models.

Peutz-Jeghers polyps from mouse models and humans were associated with STAT-3 activation and increased interleukin-6, interleukin 11, and CXCL2.

Information on current clinical trials is posted on the Internet at https://clinicaltrials.gov/. All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email:

Some current clinical trials also are posted on the following page on the NORD website: https://rarediseases.org/for-patients-and-families/information-resources/info-clinical-trials-and-research-studies/

For information about clinical trials sponsored by private sources, contact: http://www.centerwatch.com/

For information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

Supporting Organizations

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  Website: http://www.cancer.org
- Cancer.Net
  American Society of Clinical Oncology
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  Toll-free: (888) 651-3038
  Email:
  Website: http://www.cancer.net/
- Genetic and Rare Diseases (GARD) Information Center
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  Toll-free: (888) 205-2311
  Website: http://rarediseases.info.nih.gov/GARD/
- NIH/National Institute of Diabetes, Digestive & Kidney Diseases
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  Website: https://www.oncolink.org/

- Rare Cancer Alliance
  405 Holly Street
  Goodrich, TX 77335 USA
  Website: http://www.rare-cancer.org

References

JOURNAL ARTICLES
Butel-Simoes GI, Spigelman AD, Scott RJ, Vilain RE. Low-level parental mosaicism in an apparent de novo case of Peutz-Jeghers syndrome. Fam Cancer. 2018;Jun 14. doi: 10.1007/s10689-018-0093-3. [Epub ahead of print].

de Brabander J, Eskens F, Korsse SE, et al. Chemoprevention in Patients with Peutz-Jeghers Syndrome: Lessons Learned. Oncologist 2018;23:399-e33.

Jiang YL, Zhao ZY, Li BR, et al. The altered activity of P53 signaling pathway by STK11 gene mutations and its cancer phenotype in Peutz-Jeghers syndrome. BMC Med Genet. 2018;19:141.

Wang Z, Liu S, Liu S, Wang Y, Chen J, Wu B. Prenatal diagnosis in a hereditary Peutz-Jeghers syndrome family with high cancer risk. BMC Med Genet. 2018;19:66.

Chen HY, Jin XW, Li BR, et al. Cancer risk in patients with Peutz-Jeghers syndrome: A retrospective cohort study of 336 cases. Tumour Biol. 2017;39:1010428317705131.

Duan SX, Wang GH, Zhong J, et al. Peutz-Jeghers syndrome with intermittent upper intestinal obstruction: A case report and review of the literature. Medicine (Baltimore) 2017;96:e6538.

Zhang LJ, Su Z, Liu X, Wang L, Zhang Q. Peutz-Jeghers syndrome with early onset of pre-adolescent gynecomastia: a predigree case report and clinical and molecular genetic analysis. Am J Transl Res. 2017;9:2639-44.

Zhao R, Huang M, Banafea O, et al. Cronkhite-Canada syndrome: a rare case report and literature review. BMC Gastroenterol. 2016;16:23.
Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 63.
Yu J, Jiang W. Acute intussusception and polyp with malignant transformation in Peutz-Jeghers syndrome: A case report. Oncol Lett. 2015;10:1008-10.

Dai L, Fu L, Liu D, et al. Novel and recurrent mutations of STK11 gene in six Chinese cases with Peutz-Jeghers syndrome. Dig Dis Sci. 2014;59:1856-

Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: the many faces of an enigmatic disease. J Clin Pathol. 2014;67:891-7.

Urquhart P, Grimpen F, Lim GJ, et al. Capsule endoscopy versus magnetic resonance enterography for the detection of small bowel polyps in Peutz-Jeghers syndrome. Fam Cancer. 2014;13:249-55.

Wang HH, Xie NN, Li QY, Hu YQ, Ren JL, Guleng B. Exome sequencing revealed novel germline mutations in Chinese Peutz-Jeghers syndrome patients. Dig Dis Sci. 2014;59:64-71.

Resta N, Pierannunzio D, Lenato GM, et al. Cancer risk associated with STK11/LKB1 germline mutations in Peutz-Jeghers syndrome patients: results of an Italian multicenter study. Dig Liver Dis. 2013;45:606-11.

Tchekmedyian A, Amos CI, Bale SJ, et al. Findings from the Peutz-Jeghers syndrome registry of uruguay. PLoS One 2013;8:e79639.

Latchford AR, Phillips RK. Gastrointestinal polyps and cancer in Peutz-Jeghers syndrome: clinical aspects. Fam Cancer 2011;10:455-61.

van Lier MG, Westerman AM, Wagner A, et al. High cancer risk and increased mortality in patients with Peutz-Jeghers syndrome. Gut 2011;60:141-7.

van Lier MG, Mathus-Vliegen EM, Wagner A, van Leerdam ME, Kuipers EJ. High cumulative risk of intussusception in patients with Peutz-Jeghers syndrome: time to update surveillance guidelines? Am J Gastroenterol. 2011;106:940-5.

van Veelen W, Korsse SE, van de Laar L, Peppelenbosch MP. The long and winding road to rational treatment of cancer associated with LKB1/AMPK/TSC/mTORC1 signaling. Oncogene 2011;30:2289-303.

Beggs AD, Latchford AR, Vasen HF, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 2010;59:975-86.

Kopacova M, Tacheci I, Rejchrt S, Bures J. Peutz-Jeghers syndrome: diagnostic and therapeutic approach. World J Gastroenterol. 2009;15:5397-408.

Zbuk KM, Eng C. Hamartomatous polyposis syndromes. Nat Clin Pract Gastroenterol Hepatol. 2007;4:492-502.

Chow E, Lipton L, Lynch E, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology 2006;131:30-9.

Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol. 2006;4:408-15.

Zeng PY, Berger SL. LKB1 is recruited to the p21/WAF1 promoter by p53 to mediate transcriptional activation. Cancer Res. 2006;66:10701-8.

Schumacher V, Vogel T, Leube B, et al. STK11 genotyping and cancer risk in Peutz-Jeghers syndrome. J Med Genet. 2005;42:428-35.

Sweet K, Willis J, Zhou XP, et al. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA 2005;294:2465-73.

Hinds R, Philp C, Hyer W, Fell JM. Complications of childhood Peutz-Jeghers syndrome: implications for pediatric screening. J Pediatr Gastroenterol Nutr. 2004;39:219-20.

Karuman P, Gozani O, Odze RD, et al. The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death. Mol Cell 2001;7:1307-19.

Keller JJ, Offerhaus GJ, Giardiello FM, Menko FH. Jan Peutz, Harold Jeghers and a remarkable combination of polyposis and pigmentation of the skin and mucous membranes. Fam Cancer 2001;1:181-5.

Poffenberger MC et. Al. LKB1 deficiency in T cells promote the development of gastrointestinal polyposis. Science 2018; 61:406-11.

INTERNET
McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers Syndrome. 2001 Feb 23 [Updated 2016 Jul 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1266/ Accessed November 14, 2018.

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