OLSZEWSKA, Anna, MATYJA, Karolina, BERNER, Aleksandra, STENCEL, Katarzyna, STELMASZAK, Karina, MARCZYK, Klaudia, POLAK, Paulina, PĘKAŁA, Maciej, POLASZEK, Monika and BOGOWSKA, Marta. Etiology, Epidemiology, and Therapeutic Approaches for Primary Sclerosing Cholangitis in the Context of Concurrent Non-specific Inflammatory Bowel Diseases. Journal of Education, Health and Sport. 2024;60:44-57. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.60.003
https://apcz.umk.pl/JEHS/article/view/48172
https://zenodo.org/records/10658221

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.01.2023. Revised: 08.02.2024. Accepted: 14.02.2024. Published: 14.02.2024.

Etiology, Epidemiology, and Therapeutic Approaches for Primary Sclerosing Cholangitis in the Context of Concurrent Non-specific Inflammatory Bowel Diseases

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Abstract:

Introduction: Primary sclerosing cholangitis (PSC) is a chronic, idiopathic disease characterized by persistent and progressive inflammation of the intrahepatic and/or extrahepatic bile ducts. This leads to fibrosis, cholestatic complications, and liver failure. The etiology and pathogenesis of this condition are not precisely understood, although genetic and environmental factors, relying on immunological mechanisms, are considered significant.[5,7] In over 70% of patients, non-specific intestinal inflammations coexist, particularly ulcerative colitis, and sporadically Crohn's disease.[1] The therapeutic options for a permanent cure of PSC are highly limited, with liver transplantation being the only treatment option. The purpose of this study is to discuss the etiological factors, symptoms, and the relationship between PSC and IBD.[27]

Aim: Our study aimed to assess current literature on primary sclerosing cholangitis (PSC), covering its causes, symptoms, treatment methods, and the connection between PSC and inflammatory bowel disease (IBD) co-occurrence.

Materials and methods: We conducted a PubMed literature review using keywords like "primary sclerosing cholangitis pathogenesis," "primary sclerosing cholangitis and inflammatory bowel disease," and "primary sclerosing cholangitis and ulcerative colitis."

Results: Our research extensively covered PSC epidemiology, pathogenesis, and treatment options. Emphasis was placed on the heightened prevalence of inflammatory bowel diseases, including ulcerative colitis, among PSC patients.

Summary: Primary sclerosing cholangitis (PSC) is a disease causing gradual damage to bile ducts within or outside the liver. Over 70% of patients also experience inflammatory bowel disease (IBD), mainly ulcerative colitis. The exact causes of PSC and its connection to IBD remain unclear. The theories involve hyperactive "intestinal" T cells or the impact of gut microbiome on their growth. Presently, a liver transplant stands as the sole remedy.

Keywords: “P”, “psc”, “psc and ibd”, “primary sclerosing cholangitis”, “primary sclerosing cholangitis and inflammatory bowel disease”

Introduction: Primary sclerosing cholangitis (PSC) is a chronic, idiopathic disease characterized by persistent and progressive inflammation of the intrahepatic and/or extrahepatic bile ducts. This leads to fibrotic processes, cholestatic complications, and liver failure. The etiology and pathogenesis of this condition are not precisely understood, although genetic and environmental factors, particularly those based on immunological mechanisms, are believed to play a significant role.[5,7] In over 70% of patients, PSC is associated with nonspecific inflammatory bowel diseases, especially ulcerative colitis, and sporadically Crohn's disease.[1] Therapeutic options for achieving a permanent cure for PSC are severely limited, with liver transplantation being the only treatment option. The purpose of this paper is to discuss the etiological factors, symptoms, and the association between PSC and IBD. [27]

Objective of the Study:

The aim of our study was to review the current literature on primary sclerosing cholangitis (PSC). In this article, in addition to exploring the causes, symptoms, and possible treatment methods for PSC, we analyzed the correlation of inflammatory bowel disease (IBD) occurrence in patients with PSC. Materials and Methods: We conducted a literature review using PubMed with keywords such as "primary sclerosing cholangitis pathogenesis," "primary sclerosing cholangitis and inflammatory bowel disease," and "primary sclerosing cholangitis and Ulcerative Colitis." Results: In our study, we thoroughly discussed the epidemiology, pathogenesis, and available treatment methods for patients with PSC. We also focused on the increased frequency of concomitant inflammatory bowel diseases, including ulcerative colitis, in these patients.

Summary:

Primary sclerosing cholangitis is a disease characterized by progressive destruction of intrahepatic and/or extrahepatic bile ducts. In over 70% of patients, it is associated with nonspecific inflammatory bowel disease, most commonly ulcerative colitis. The pathogenesis of PSC, as well as its connection to the coexistence with IBD, is not precisely understood. Hypotheses have been proposed involving overactive "intestinal" T lymphocytes or the influence of the gut microbiome on their development. Currently, liver transplantation is the only treatment method. Keywords: "primary sclerosing cholangitis pathogenesis," "psc," "psc

and ibd," "primary sclerosing cholangitis," "primary sclerosing cholangitis and inflammatory bowel disease"

1.Introduction: Primary sclerosing cholangitis is a chronic cholestatic liver disease characterized by inflammatory and fibrotic changes that result in multifocal strictures of intrahepatic and extrahepatic bile ducts. The pathogenesis of PSC is not precisely understood. A distinctive feature of PSC is its association with nonspecific inflammatory bowel diseases, most commonly ulcerative colitis, to a lesser extent Crohn's disease or unspecified inflammatory bowel diseases. Additionally, there is an increased risk of developing gastrointestinal malignancies, primarily bile duct cancer, gallbladder cancer, and colorectal cancer, with over 70% of PSC patients having concurrent IBD. PSC is a rare disease, with an incidence ranging from 2 to 16 per 100,000.[5] Both the prevalence and incidence are steadily increasing, potentially attributed to improved access to medical care and diagnostics. It is noteworthy that recent decades have seen a heightened occurrence of autoimmune-related diseases. [27] PSC affects individuals of both genders and can manifest at any age, though it predominantly afflicts males, with an average age of onset between 30 and 40 years. It is a progressive disease, and more than 40-50% of patients require liver transplantation within 10-15 years of the first symptoms. Approximately 25% of patients also exhibit other autoimmune diseases. The siblings of individuals with PSC and IBD face a tenfold and fivefold increased risk of developing PSC and IBD, respectively, underscoring the significant influence of genetic factors on pathogenesis. [5, 17]

Pathogenesis: The pathogenesis of PSC is not precisely understood, but it is recognized as a disease developing on an autoimmune basis.[24] In some patients, elevated levels of antibodies against neutrophil cytoplasm, antinuclear antibodies, and anticardiolipin antibodies have been observed. Analyzing the pathogenesis has involved studying the impact of over 20 genes on the development of PSC, with environmental factors (>50%) having the greatest influence, while genetic factors contribute only 10%.[24] Genetic studies have identified an increased risk of developing this disease in individuals expressing the HLA B8, HLA DR3, and HLA 48 alleles.[2, 7, 11, 12] For many years, the association of PSC with various factors and the coexistence of inflammatory bowel diseases in such a large group of PSC patients have directed hypotheses toward the influence of gut microbiota or excessive stimulation of "intestinal" T lymphocytes. The gut microbiota hypothesis is based on the passage of microbial fragments into the liver through portal circulation, inducing an abnormal immune response. The second hypothesis suggests excessive stimulation of lymphocytes in the gut lymphoid tissue and their subsequent negative impact on the immune response,

leading to damage to bile ducts and intestines. This results from the overlap of identical adhesion molecule particles of mucosal-vascular endothelial cells and the expression of VCAM1. [1, 2, 5, 25, 11, 12, 13, 17]

Research also explores the influence of cholangiocytes themselves on the development of PSC in genetically predisposed individuals by secreting pro-inflammatory cytokines (physiologically, cholangiocytes secrete, among others, TNF-alpha, IL-6, IL-8) or stimulating T lymphocytes, indicating the autoimmune basis of this disease. [2, 4, 5, 25] Significant importance is attributed to defects in mechanisms protecting against the toxicity of bile acids. Confirmation of the involvement of bile acids in the development of IBD and PSC can also be found in the more frequent involvement of the right part of the intestines, where the concentration of these acids is higher. The composition of bile is shaped by the catabolism of intestinal-microbiological (enterohepatic) circulation. Changes in gut microbiota, specifically its depletion, are also observed in PSC, but it is unclear whether this change is a cause or consequence of the disease. Recent studies utilizing antibiotic therapy in treatment lean towards the participation of pathological gut microbiota, initiating the development of PSC. When examining the genetic basis of PSC, the strongest association has been shown with HLA on chromosome 6 (the risk of development is about 3-5 times higher compared to the general population), while other genes exhibit weaker correlations. Researchers have also noted increased susceptibility to PSC in genes in the interleukin-2 pathway (CD28, IL-2, IL-2 receptor alpha subunit). Such studies suggest the influence of acquired immunity and T lymphocytes on pathogenesis. [5, 15, 16] A limited genetic association between PSC and IBD has been demonstrated, where fewer than 10 out of 150 genes are interconnected. Based on these findings, some scientists argue that IBD and PSC should be considered as separate disease entities. It cannot be determined whether the coexistence of IBD and PSC is caused by exposure to the same antigen triggering an immune response simultaneously in the intestines and bile ducts or if the inflammatory process results from the recruitment of T lymphocytes activated in the gut lymphoid tissue into the liver. [11, 12, 13, 24]

It has also been shown that other genes in individuals with PSC increase susceptibility to other autoimmune diseases, including type 1 diabetes. [24, 1, 2] Studies have not been able to determine the exact triggering factors for PSC. Researchers observed a protective effect of smoking.[2] In one study, it was found that individuals with PSC consumed less coffee than the general population, while in other studies, they consumed more red meat (steaks, hamburgers) and less fish. This study suggested a significant influence of dietary habits and food preparation methods on the risk of developing PSC. [2, 3] Course: The natural course of

PSC is progressive and leads to fibrosis of the bile ducts, followed by liver failure, cirrhosis, or even the development of bile duct cancer. The prognosis for patients who are asymptomatic at the time of diagnosis is better than for patients with symptoms. Biochemical tests assessing liver function, ALP, and bilirubin vary over the course of the disease, making it difficult to assess the stage of the disease and the overall prognosis. Evaluation and diagnosis are possible precisely based on liver biopsy and MRCP. Symptoms: In recently published studies, it has been shown that approximately 50% of patients have symptoms. The most common complaints are itching, pain in the right upper quadrant of the abdomen, fatigue, jaundice, and even weight loss. Advanced PSC symptoms additionally include gastrointestinal bleeding, ascites, and encephalopathy as a consequence of liver failure and cirrhosis. [1, 5, 22, 23] Physical examination may reveal jaundice, skin scratches due to persistent itching, as well as hepatomegaly (44%) and splenomegaly (39%). [5, 22, 10] The quality of life for these patients is severely limited, resulting from the recurrent inflammation of the bile ducts that is challenging to treat, persistent itching unresponsive to standard methods, and a constant feeling of fatigue for which there is no effective therapy. At the time of PSC diagnosis, most patients are asymptomatic and diagnosed due to incidentally detected abnormal liver parameters or for other reasons. Symptoms may appear later as PSC progresses.

Diagnosis:

In biochemical tests, the level of ALP is elevated, and the activities of aspartate and alanine transaminases are increased 2-3 times above the upper limit of normal. Bilirubin and albumin levels may be normal in the early stages of the disease. About 10% of patients exhibit an elevated level of IgG4 in the serum, and these patients have a poorer prognosis. [5, 23] For PSC diagnosis, MRCP (Magnetic Resonance Cholangiopancreatography) is utilized as the gold standard, and ERCP (Endoscopic Retrograde Cholangiopancreatography) or PTC (Percutaneous Transhepatic Cholangiography) can also be used. ERCP is more invasive than MRCP, but its diagnostic accuracy is similar. PTC is reserved for patients with contraindications to MRCP and ERCP. Characteristic features of PSC in imaging studies include numerous strictures separated by dilated segments of intrahepatic and/or extrahepatic bile ducts. [5, 4, 3, 27] Liver biopsy is not indicated if imaging results are typical for PSC. It is performed when imaging studies are normal but PSC is suspected, and it is also necessary when there is suspicion of the PSC-AIH variant or coexisting diseases. Autoimmune hepatitis (AIH) can occur in about 6-10% of patients. Interestingly, studies have shown that these

patients have the same risk of liver and bile duct disease progression but a lower risk of developing malignancies in both the liver and bile ducts. [2, 25, 26]

PSC and IBD:

Inflammatory bowel disease (IBD), whether ulcerative colitis or Crohn's disease, typically affects the large intestine, especially the right side, sparing the rectum. Therefore, ileocolonoscopy is necessary for patients with PSC. During IBD examinations coexisting with PSC, a milder course and even a normal appearance of the intestine in endoscopic studies have been observed, which can complicate the diagnosis. [14] Regular colonoscopy with biopsy for histopathological examination is also recommended due to the increased risk of developing colorectal cancer. [5] Patients with PSC and IBD, despite the milder course of inflammatory bowel disease, are at a higher risk of developing cancer than patients with isolated IBD. [9]

Complications and prognosis:

PSC is a progressive disease, and there is no effective treatment method.

PSC patients are exposed to numerous complications, such as:

- Deficiencies in fat-soluble vitamins (A, D, E, K)
- Osteoporosis
- Bile duct inflammation
- Gallstones
- PSC is a disease that leads to gradual liver fibrosis and, consequently, cirrhosis, portal hypertension, and an increased risk of hepatocellular carcinoma. [3]

The risk of colorectal cancer in patients with PSC and IBD is five times higher than in patients with IBD without PSC, so studies suggest regular colonoscopy from the time of PSC diagnosis. Patients also more frequently develop hepatocellular carcinoma (HCC), pancreatic cancer, bile duct, and gallbladder cancer. The risk of HCC with PSC is lower than with cirrhosis of the liver due to other causes. [5, 17, 24] In about 5% of patients, the presence of gallbladder polyps is observed, of which 55-75% are malignant tumors.

Bile Duct Cancer:

Distinguishing symptoms of PSC from early stages of Cholangiocarcinoma (CCA) can be challenging. It is important to note that early stages of cancer usually progress without symptoms, whereas rapid deterioration of liver function and increasing jaundice, abdominal pain, and weight loss in PSC patients should raise suspicion of CCA. The risk of developing CCA in patients with PSC is four times higher than in the general population. In studies, the

main causes of death were CCA (32%), complications related to transplantation (9%), and colorectal cancer (8%). [5, 17, 18, 19, 27, 28]

Liver Transplantation:

Due to the progressive nature of PSC, approximately 40% of patients ultimately require a liver transplant. Indications for liver transplantation are similar to other liver diseases based on the MELD scale. Transplantation provides a 5-year survival rate of 80% for patients, but PSC recurs in about 25%. The eligibility for this procedure varies by country; in Scandinavia, transplantation is performed in patients with bile duct dysplasia, while in some American centers, it is only done in patients with hilar CCA. The percentage of transplants for PSC patients is less than 5% in the USA, while it's around 15% in Scandinavia. [18] These patients show lower mortality and better outcomes after liver transplantation compared to patients qualifying for other reasons. Remission of IBD is recommended before transplantation, but after the operation and during immunosuppression, relapses and exacerbations of IBD often occur in about one-third of cases. Some researchers suggest considering colectomy due to the active disease in these patients and the increased risk of developing colorectal cancer, as well as recurrence of PSC despite transplantation. However, this is not performed routinely. [3, 18, 17, 20]

Treatment:

Currently, there is no available cure for primary sclerosing cholangitis (PSC). Early detection, prevention of complications, and avoiding the development of liver failure and subsequently cirrhosis are crucial in managing this disease. The only known treatment method is liver transplantation. Ursodeoxycholic acid (UDCA) has been studied in the treatment of primary sclerosing cholangitis. Research has shown that patients receiving UDCA exhibited reduced levels of serum aminotransferases, but it did not affect their life expectancy. In another study, patients receiving high doses of UDCA had an increased risk of progression to liver failure and cirrhosis, the need for transplantation, and even death. Data on UDCA treatment are conflicting, and the American societies do not endorse its use in PSC treatment. Currently, research is ongoing on fecal microbiota transplantation and antibiotic therapy in PSC, exploring the impact of the gut microbiome on the development of this disease [8, 5, 6, 18, 15].

Conclusion:

Primary sclerosing cholangitis (PSC) is an autoimmune disease characterized by progressive destruction of intrahepatic and/or extrahepatic bile ducts. The pathogenesis of PSC is not fully understood, but research has shown the influence of genetic and environmental factors

on its development. Interestingly, environmental factors appear to play a greater role in PSC development than genetic susceptibility. Hypotheses have been proposed regarding the gut microbiota, excessive stimulation of T lymphocytes in gut lymphoid tissue, and the impact of cholangiocytes and bile acids on PSC development. The action of environmental factors in predisposed individuals leads to cholangiocyte damage, inflammation, and subsequent fibrosis of the bile ducts. There is also observed depletion of the gut microbiome composition, but researchers are uncertain whether it is a cause or effect of PSC. More than 70% of patients with PSC also have concurrent inflammatory bowel disease (IBD), most commonly ulcerative colitis. IBD tends to be milder in these patients, often affecting the right side of the intestine, but PSC-IBD patients have an increased risk of developing colorectal cancer compared to those with isolated IBD. Additionally, around 25% of PSC patients exhibit coexistence of other autoimmune diseases such as type 1 diabetes. Investigating the frequent occurrence of PSC-IBD, researchers have analyzed the genetic basis and the influence of shared environmental factors initiating pathological processes. Limited genetic association between these two diseases has led researchers to hypotheses involving the gut microbiota, the hyperactivity of intestinal T lymphocytes, and the irritating effects of bile acids, particularly on the right side of the intestine. PSC is a progressive disease, and apart from liver transplantation (with a 25% risk of PSC recurrence), there is currently no effective treatment method to influence its course. The disease leads to complete destruction of the bile ducts, liver failure, and cirrhosis. PSC patients are prone to fat-soluble vitamin deficiencies, osteoporosis, and an increased risk of developing bile duct cancer (HCC). Colorectal cancer risk is also elevated, given the frequent coexistence of IBD. Regular abdominal ultrasound and colonoscopy are recommended for monitoring. IBD can manifest at any point in the disease, even after liver transplantation. Research into the pathogenesis of PSC and the search for an effective treatment method are ongoing.

Author’s contribution:

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All authors have read and agreed with the published version of the manuscript

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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