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Sclerosing cholangitis in immunocompromised patients associated with *cryptosporidium* infection

Colangite esclerosante em pacientes imunocomprometidos associada à infecção por cryptosporidium

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ABSTRACT: *Introduction*: *Cryptosporidium* is a protozoan who parasites the gastrointestinal tract, with a significantly higher incidence in children than in adults. It mainly infects the small intestine and causes acute diarrhea in immunocompetent patients. However, in immunocompromised patients, cryptosporidiosis can be a severe and chronic disease with persistent symptoms, and cause atypical manifestations, such as atypical gastrointestinal disease, biliary tract disease, respiratory tract disease and pancreatitis. *Cryptosporidium parvum* infection appears to be strongly associated with the development of cholangitis. Nonetheless, the available treatment modalities are limited, and prevention and risk reduction should be the main interventions. *Objective***:** Report the current knowledge landscape and provide information on cholangitis associated with cryptosporidiosis in immunosuppressed patients in the pediatric age, thus contributing to the diagnosis and therapeutic behaviors. *Methodology***:** It was reviewed the main databases: Institute of Health PUBMED, Scientific Electronic Library Online (SciELO) - searching for articles that considered the subject and using and crossing the descriptors: Cholangitis, Immunodeficiency, Cryptosporidiosis, Pediatrics. Articles were searched in Portuguese, English and Spanish, containing texts from 2001 to 2018. *Discussion***:** The suspicion of chronic liver disease arises with the appearance of considerable hepatomegaly and laboratory abnormalities (hepatic transaminases, alkaline phosphatase and gamma GT with increased serum levels) in patients with previous immunodeficiency diagnosis. Several studies have shown that the therapeutic arsenal - antiparasitic agents and macrolide antibiotics - was not effective in eradicating infection and preventing the progression of the disease. Therefore, liver transplantation becomes necessary with the evolution of the disease. However, not even the procedure is capable of improving the survival rates of this group of patients, due to the complications of the procedure, such as absence of immunocompetence, use of medications, or graft rejection**.** Recurrence can reach a fifth of patients. *Conclusion***:** Sclerosing cholangitis secondary to cryptosporidiosis should be considered in the differential diagnosis of chronic liver disease in children. Diagnosis can be made by demonstrating cholangiographic features change of the bile duct associated with protozoal infection in the hepatic and biliary tract. Such changes in children are often subtle. Therefore, prospective, controlled and collaborative trials in patients with cryptosporidiosis sclerosing cholangitis are necessary to provide a better understanding of the prevalence, pathogenesis, potential treatment and prognosis.

Keywords: Cholangitis; Immunodeficiency; *Cryptosporidiosis;* Pediatrics.

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RESUMO: *Introdução: Crytosporidium* é um protozoário parasita do trato gastrointestinal, com incidência significativamente maior em crianças do que em adultos. Infecta, principalmente, o intestino delgado e provoca diarreia aguda em imunocompetentes. Entretanto, em pacientes imunocomprometidos, a criptosporidiose pode ser uma doença grave e crônica com sintomas persistentes, além de causar manifestações atípicas, como doença gastrintestinal atípica, doença do trato biliar, doença do trato respiratório e pancreatite. A infecção por *Cryptosporidium parvum* parece estar fortemente associada ao desenvolvimento de colangite. No entanto, as modalidades disponíveis de tratamento são limitadas, devendo a prevenção e redução de risco configurarem as intervenções principais. *Objetivo:* Relatar o panorama de conhecimentos atuais e prover informações sobre colangite associada à criptosporidiose em pacientes imunodeprimidos na faixa etária pediátrica contribuindo desta forma para o diagnóstico e condutas terapêuticas. *Metodologia:* Foi feita uma revisão nas principais bases de dados, Institute of Health PUBMED, Scientific Electronic Library Online (SciELO), utilizando descritores, buscando artigos que contemplassem os assuntos: Colangite, Imunodeficiência, Criptosporidiose, Pediatria, sendo realizado o cruzamento entre eles. Foram pesquisados artigos nas línguas portuguesa, inglesa e espanhola, contendo textos compreendidos entre o período de 2001 a 2018. *Discussão:* A suspeita da doença hepática crônica surge com o aparecimento de hepatomegalia considerável e de alterações laboratoriais (transaminases hepáticas, fosfatase alcalina e gama GT com níveis séricos aumentados) em pacientes com diagnóstico prévio de imunodeficiência. Diversos trabalhos mostraram que o arsenal terapêutico – de agentes antiparasitários e antibióticos macrolídeos - não foi eficaz para erradicar a infecção e impedir a progressão da doença. Dessa forma, o transplante hepático se faz necessário com a evolução da doença. No entanto, nem mesmo o procedimento é capaz de melhorar os índices de sobrevida deste grupo de pacientes, devido às complicações inerentes ao transplante, como ausência de imunocompetência, uso de medicações e, rejeição do enxerto. A recorrência pode chegar a um quinto dos pacientes. *Conclusão:* A colangite esclerosante secundária à criptosporidiose deve ser considerada no diagnóstico diferencial de doença hepática crônica em crianças. O diagnóstico pode ser feito pela associação da infecção pelo protozoário na via hepática e biliar com alterações colangiográficas características do ducto biliar. Tais alterações em crianças são, frequentemente, sutis. Portanto, ensaios prospectivos, controlados e colaborativos em pacientes com colangite esclerosante por criptosporidiose são necessários para fornecer uma melhor compreensão da prevalência, patogênese, possível tratamento e prognóstico.

Descritores: Colangite; Imunodeficiência; Criptosporidiose; Pediatria

INTRODUCTION

Cryptosporidium is a protozoan parasite of the gastrointestinal tract with different degrees of pathogenicity and virulence in humans, that is, there are a variety of pathogenic factors that affect the occurrence and outcome of the disease, particularly in cases of opportunistic infections associated with a compromised imune system of the host[1]. The first records of infection by this protozoan were in mid-1976 in patients with severe watery diarrhea, which later gained more importance with the condition of HIV patients during the early 1980s, which led to the inclusion of cryptosporidiosis as an AIDS-defining disease[1,5].

Currently, it corresponds from 1 to 3% of the cases of immunocompetent patients with diarrhea in industrialized countries and 7 to 10% in developing countries, with a significantly higher incidence in children than in adults. It is known as an important parasite transmitted by water and contaminated food that mainly infect the small intestine[1,2] and cause transient and self-limited acute diarrhea, lasting about 2 to 3 weeks in immunocompetent patients. Other symptoms associated include nausea, vomiting, and low fever[5]. However, in immunocompromised patients, cryptosporidiosis can be a serious and chronic disease, with persistent symptoms that lead to dehydration, besides causing atypical manifestations such as atypical gastrointestinal disease, biliary tract disease, respiratory tract disease and pancreatitis. Because there are no pathognomonic signs or symptoms, laboratory diagnosis is necessary by finding oocysts in stool samples by microscopic examination, immunofluorescence, or identification of Polymerase chain reaction (PCR) DNA of the parasite[9].

Cryptosporidium causes apoptosis of the biliary epithelium in humans and, for this reason, may be related to the development of sclerosing cholangitis. In addition, it has been seen that inflammation caused by the parasite can generate an immune system dysregulation[6]. The infected biliary tree constitutes a source of the parasite through which cryptosporidiosis can recur, in addition to protecting the protozoan from the action of luminal antiparasitic agents, such as paromomycin, requiring the use of drugs with biliary excretion, such as nitazoxanide, for its treatment[5,9].

The available treatment modalities are limited[9]. Therefore, prevention and reduction of contamination risk are the main interventions. Cryptosporidiosis is a highly contagious disease from person to person, since large numbers of oocysts are excreted in stools. Thus, personal hygiene is essential to limit contagion, especially in the group of immunosuppressed patients.

OBJECTIVE

To report the current knowledge overview of cholangitis associated with cryptosporidiosis in pediatric patients with primary immunodeficiencies, thus contributing to the diagnosis and therapeutic approaches.

METHODOLOGY

This literature review was developed through search on sites that provide official articles, whose consultation is public and open access in addition to search in the following databases: Institute of Health PUBMED, Scientific

Electronic Library Online (SciELO), using the descriptors: Cholangitis, Immunodeficiency, Cryptosporidiosis, Pediatrics, being performed the crossing between them. Articles were searched in Portuguese, English and Spanish, containing texts between 2001 and 2018, and others when necessary due to their great relevance to the research. Twelve articles involving the theme were found, and after reading them, three that did not have a relationship with the desired theme for this review were excluded.

RESULTS

This literature review aimed to gather the most current studies that associate the cause of primary sclerosing cholangitis in immunodeficient children with *Cryptosporidium* protozoan infection. There are few case reports on the subject in the pediatric population and little is known about an effective treatment for this pathology, because it is difficult to select a drug that acts in the biliary pathway where the parasite remains in latent form.

Among the articles already published on the subject, after crossing the descriptors used, 9 articles with a better approach to the theme were selected, because they contained children already with the declared diagnosis of sclerosing cholangitis at the same time when co-infection with the parasite was diagnosed. In summary form, we describe each work cited in table form (Table 1). In general, however, the fact that there are no concrete measures in relation to the therapeutic plan for this pathology, although new studies relate transplantation as a curative method, it's clear the need for further studies related to the theme. Although such an association is rare, it can be lethal when it reaches the pediatric population more markedly, since the infection is more prevalent in children.

Table 1. Articles contemplated in this review **Table 1.** Articles contemplated in this review

Authors	Patients and methods	Results and conclusions
Bouzid et al.	Review Article	There are currently more than 25 putative virulence factors, mainly identified in molecular techniques. Knowledge of certain host factors that are associated with variations in both severity and risk of infection has increased dramatically.
Wolska-Kusnier et al.	A group of 5 patients with genetically confirmed type 1 hyper-IgM syndrome and one patient with primary CD4 lymphopenia were included in the study.	Chronic cryptosporidiosis was confirmed in 3 patients with genetically confirmed hyper-IgM syndrome type 1 and in one patient with primary CD4 lymphopenia. Molecular diagnosis showed the presence of C *parvum*, C *hominis* and C *meleagridis* in the analyzed specimens. *Cryptosporidium* infection with severe clinical symptoms seen in patients with hyper-IgM syndrome requires repeated and regular screening in this group of patients.
Mieli-Vergani, Vergani	Review Article	The diagnosis of liver disease is related to about 1-10 years of immunodeficiency diagnosis. Early discovery provides the use of Immunoglobulin and antibiotics to prevent infections, but involvement with sclerosing cholangitis remains unaffected by anti-infectious strategies.
Feldstein et al.	A longitudinal cohort study was to determine the long-term outcome of children with primary sclerosing cholangitis (PSC). Fifty-two children with PSC confirmed by cholangiography (34 boys and 18 girls; mean age of 13.8 +/- 4.2 years; interval, 1.5-19.6 years) who were attended at the institution for a period of 20 years were followed for up to 16.7 years.	Two thirds had symptoms and/or signs of primary sclerosing cholangitis and 81% had concomitant inflammatory bowel disease. Twenty-five percent had total alkaline phosphatase activity within the normal age range, but all had high levels of gamma-glutamyl transpeptidase. Autoimmune hepatitis superimposed with primary sclerosing cholangitis was present in 35% of children. A positive but transient clinical and/or biochemical response occurred under ursodeoxycholic acid therapy, alone or in combination with immunosuppressive drugs. During follow-up, 11 children underwent liver transplantation for end-stage PSC and 1 child died. The median (50%) liver transplant-free survival was 12.7 years. Compared to a US population with corresponding age and gender, survival was significantly lower in children with PSC ($P<0.001$). In a Cox regression model, lower platelet count, splenomegaly, and older age were associated with lower survival. Presence of autoimmune hepatitis superimposed with PSC ($P = 0.2$) or medical therapy ($P = 0.2$) did not affect survival. In conclusion, primary sclerosing cholangitis significantly decreases survival in this infant population. Although pharmacological therapy can initially improve liver test symptoms and results, it does not seem to affect the outcome in the long run.
Chalmers Davies	This literature review covers the life cycle, pathogenesis, clinical presentations, diagnosis, prevention and management of cryptosporidiosis in humans.	*Cryptosporidium* has emerged as an important cause of diarrheal disease worldwide, especially among young children and patients with immunodeficiencies. Generally presenting as a syndrome similar to gastroenteritis, the disease varies from serious to severe and the signs and symptoms depend on the site of infection, the nutritional and immunological status of the host, and parasite-related factors. Sources and routes of transmission are multiple, involving both zoonotic and anthroponotic dissemination, and facilitated by the resistance of the parasite to many commonly used disinfectants. Prevention and control measures are important for the protection of vulnerable groups, since treatment options are limited.

Table 1. Articles contemplated in this review

Authors	Patients and methods	Results and conclusions
Baran et al.	Case report of a new homozygous frame displacement mutation in the IL21R gene of a patient with T-, B- and natural killer (NK) cell lymphopenia.	A new biallelic function loss mutation affecting the IL21R gene has been identified in a patient with combined immunodeficiency. In contrast to previous studies, the patient had marked CD4 and NK lymphopenia. Thus, the phenotype of IL21 deficiency (receptor) may be considerably more diverse than previously appreciated, and molecular analysis of patients with unclear genetic etiology of combined immunodeficiency should include IL21 (receptor) genes.
Paolla et al.	Case report	A strictly sequential strategy, with a sequential liver transplant free of surgical complications, followed by a reduced intensity conditioning, allowed hematopoietic stem cell transplantation to be performed only one month after transplantation, preventing the recolonization of the liver graft by *Cryptosporidium parvum*. sequential liver transplantation and combined sequential hematopoietic stem cell transplantation resolved cirrhotic evolution and corrected immunodeficiency, so that the infection responsible for progressive sclerosing cholangitis did not repeat.
Rahman et al.	Case report of a 43-year-old man with hyper-immunoglobulin M syndrome due to CD40 binder deficiency presented insidious onset of recurrent diarrhea and disordered liver function tests.	Standard stool microscopy was repeatedly negative for cryptosporidia, but immunofluorescent testing and polymerase chain reaction eventually demonstrated the presence of infection. Despite paromomycin and nitazoxanide, he developed sclerosing cholangitis secondary to cryptosporic infection. Cholangiocarcinoma was found on imaging after three biopsies of a suspected lesion. This is a rare complication of this immunological deficiency predominantly combined in children who have not previously been reported in a long-term survivor with this condition.
Hunter, Nichols	Review examining the impact of cryptosporidiosis on patients with various immunosuppressive conditions, so guidance groups need to take steps to reduce the risk of disease can be better defined.	In the immunodeficient group, HIV patients who were treated for parasite eradication had better responses than patients with sclerosing cholangitis with cryptosporidiosis. In addition, symptoms may become milder with antiretroviral therapy that restores the immune functioning of HIV-infected patients

DISCUSSION

Cholangitis associated with infection by the protozoan Cryptosporidium does not have a defined incidence in the literature, but several reports point to a higher prevalence in children with immunodeficiencies. Wolska-Kusnierz et al.[2] verified in immunodeficient patients the presence of *Cryptosporidium* associated with cholangitis, in a study that followed 6 pediatric patients between 13 months and 11 years. Four children were diagnosed with crisptosporidiosis through the finding of parasite oocysts in stools and immunofluorescence studies and with diseases in the hepatic and biliary tract, while the other two had immunodeficiencies, but the presence of protozoa was not verified. Thus, the appearance of sclerosing cholangitis and inflammation of the bile duct was identified as a manifestation of the infection.

Chronic infection or inflammation of the bile ducts due to Cryptosporidiosis is probably strongly related to the development of malignancy in the biliary tract. Tumors in most cases are preceded by chronic cholangiopathy and even liver cirrhosis[2,8]. The genetic mutation in the IL21-R gene was related to predisposition to cholangitis after infection in patients with combined immunodeficiency[6].

Mieli-Vergani and Vergani[3] reported that the diagnosis of liver disease is frequently made after about 1-10 years of immunodeficiency diagnosis. Early discovery leads to the use of Immunoglobulin and antibiotics to prevent infections, but development of sclerosing cholangitis remains unaffected by anti-infectious strategies.

Thus, the suspicion of chronic liver disease arises with the appearance of considerable hepatomegaly and laboratory changes (hepatic transaminases, alkaline phosphatase and GT gamma with increased serum levels)[3], evidence of increased gallbladder, dilation of the intra- and extrahepatic bile ducts observed in imaging tests, in addition to histological confirmation through liver biopsy. *Cryptosporidium parvum* infection appears to be strongly associated with the development of cholangitis, and can even lead to complications such as cholangiocarcinoma[8], especially in patients with hyper-IgM syndrome[7,9]. Such a syndrome is considered a clinical variant of hypogammaglobulinemia, a severe immunodeficiency with significant T-cell impairment and mutations in the CD40 binding gene. It has high mortality and chronic diarrhea and liver involvement (both often associated with *Cryptosporidium* infection)[9].

Immunodeficient patients followed for decades, with cholangitis confirmed by magnetic resonance imaging and cholangiography, were cured with transplantation, but the success of treatment is hampered by the use of medications, or graft rejection[2]. Currently, however, success in hematopoietic stem cell transplantation has been reported in a 7-year-old patient with immunodeficiency and sclerosing cholangitis, already with cirrhosis, with the presence of *Cryptosporidium* in the bile ducts[7].

Several antibacterial and antiparasitic agents have shown efficacy, although not complete, against the parasite. They are: azithromycin, paromomycin and nitazoxanide[9]. However, clinical trials have shown that, despite treatment,

eradication is not achieved[2]. In the immunodeficient group, HIV patients who were treated for parasite eradication had better responses than patients with sclerosing cholangitis with cryptosporidiosis. In addition, symptoms may become milder with antiretroviral therapy that restores the immune functioning of HIV-infected patients[9].

In parallel with sclerosing cholangitis of noninfectious cause, Feldstein et al.[4] indicates the treatment of primary sclerosing cholangitis in children with the use of Ursodeoxycholic acid, although, this does not limit the progression of liver disease, although it provides clinical and laboratory improvement for most patients. Thus, the use does not affect the survival of these children, who already have a shorter life expectancy than other children of the same age, and liver transplantation is often necessary. However, there are no studies confirming the efficacy in the treatment of Ursodeoxycholic acid in children with sclerosing cholangitis associated with *Cryptosporidium infection,* leaving transplantation as a therapeutic alternative in refractory cases to the use of antiparasitics. This makes clear the need to research alternatives so that drug therapy is well defined for the treatment of this group of immunodeficient patients, preferably involving both primary and infectious cholangitis, in addition to the follow-up of patients already transplanted.

CONCLUSION

Cholangitis associated with cryptosporidiosis should be considered in the differential diagnosis of chronic liver disease in children, especially immunodeficient patients. The incidence of this condition in immunosuppressed patients is poorly described in the literature in general. However, the fact that it does not present effective treatment in both patients with congenital and acquired immunodeficiencies, alerts to the need for further studies on the subject. The diagnosis can be made by demonstrating colangiographic alterations characteristic of the bile duct and the finding of the protozoan by culture and PCR, or biopsy demonstrating the parasite in the hepatic/biliary tract[7]. Thus, prospective, controlled and collaborative trials in patients with infectious sclerosing cholangitis are necessary to provide a better understanding of prevalence, pathogenesis, possible treatment and prognosis.

Participação dos autores: Informamos para devido fins que o artigo foi confeccionado em conjunto pelo grupo de autores com o grau de participação seguinte: *Raquel, Gessianni e Gustavo* - pesquisa dos artigos, leitura e exclusão de pesquisas não pertinentes ao envolvimento do tema escolhido; *Gessianni e Raquel* - Cruzamento de informações, leitura e escrita do conteúdo; *Lígia e Mayra* - Orientação organizacional e sobre a essência, argumentação e relevância do trabalho: *Lígia, Mayra, Gessienne* - revisão do texto quanto a integridade e veracidade quanto as fontes utilizadas. Dessa forma, o grupo de autores certifica participação conjunta na confecção do artigo, esperando contribuir no tema em questão, com uma síntese sobre o assunto em pontos atuais de conduta e definições baseado em trabalhos anteriores validados e publicados em revistas reconhecidas.

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