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Doença de Whipple e fator de risco em três relatos de caso

| Whipple's disease and risk factor in three case reports

RESUMO | Introdução: *A Doença de Whipple é uma doença infecciosa crônica causada pela bactéria Tropheryma whipplei e é caracterizada por diarreia, artralgia, perda de peso e distúrbios neurológicos. A infecção ocorre mais frequentemente em pacientes imunossuprimidos.* **Relato de caso:** *A doença de Whipple foi diagnosticada em três homens caucasianos. Dois com histórico de dependência de álcool, um deles com cirrose hepática e outro era funcionário da drenagem de esgoto. O terceiro paciente foi que não apresentava fator de risco óbvio. Identificar fatores imunossupressores e o contato repetitivo de fezes podem ajudar no diagnóstico.* **Conclusão:** *A Doença de Whipple, por ser rara e com sintomatologia variável, necessita de suspeição médica para o diagnóstico precoce proporcionar tratamento reduzindo morbimortalidade e sequelas neurológicas.*

Palavras-chave | *Tropheryma whipplei; Doença de Whipple; Diarréia; Troferima.*

ABSTRACT | Introduction: Whipple's Disease is a chronic infection disease caused by the bacterium *Tropheryma whipplei* and is characterized by diarrhea, arthralgia, weight loss and neurological disorders. The infection occurs more frequently in immunosuppressed patients. **Case report:** Whipple's Disease was diagnosed in three Caucasian mans. Two with alcohol dependence history, one of them with hepatic cirrhosis and another was a sewage drainage worker. The third patient was who have no obvious risk factor Identify immunosuppressive factors and repetitive stools contact can help in the diagnosis. **Conclusion:** Whipple's Disease, being rare and with variable symptomatology, needs medical suspicion to diagnose early provide treatment reducing morbimortality and neurological sequelae.

Keywords | Tropheryma whipplei; Whipple Disease; Diarrhea; Tropheryma.

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INTRODUCTION|

Whipple's Disease (WD) is a chronic infection disease caused by the bacterium *Tropheryma whipplei* and is characterized by diarrhea, arthralgia, weight loss, neurological disorders, fever, anaemia and adenopathy[1,3]. The first case was described in an autopsy in1907 by George Whipple. In 2003 was made a review using tissues obtained from the 1907 autopsy and *Tropheryma whipplei* could still be detected[2]. Between 1907 and 1987 were reported 696 cases of Whipple's Disease and after 1980 the incidence is about 30 cases/year worldwide[1]. Indirect evidence indicates the prevalence in 1/1.000.000 persons[3]. A few cases were reported in Brazil and, as it is not a compulsory reported disease, it is difficult to estimate the prevalence and incidence. This shows how extremely rare this disease is. Table 1 shows the case reports found when the words "Brasil" or "Brazil" and "Doença de Whipple" or "Whipple disease" are searched in Scielo, Pubmed and Google academic platform.

Tropheryma whipplei was already identified in land, water and seawater sediments. Its detection is about 0,2% in healthy people. This disease has several clinical presentations. Auto limited acute infections can occurs on respiratory tract or gastrointestinal. In counterpart, chronic infection (Whipple's Disease) needs genetic predisposition (HLA DRB1*13 e DQB1*6)[3,13]. Classical symptoms are diarrhea, arthralgia and weight loss but they can show up with neurological disorders, fever, anaemia and adenopathy[3]. Whipple's Disease develops over years or decades after the infection by *Tropheryma whipplei* due to its insidious replication. This disease characteristically affects Caucasians men (male-to-female ratio is about 8:1) with mean age at onset 50 years[1,3].

This report has the objective to present three cases of Whipple's Disease diagnosed in Cassiano Antônio Moraes University Hospital of the Federal University of Espírito Santo. The objective is to expand the knowledge of this disease and alert health professionals about the possibility of this diagnosis in Brazil, to carry out early diagnoses and treatments to contain possible complications and reduce morbidity and mortality.

METHODS|

This is a case series of 3 patients with WD who was hospitalized in the gastroenterology ward of Cassiano Antônio Moraes University Hospital of the Federal University of Espírito Santo. The following information was obtained: demographic characteristics, symptoms, physical examination, medical history, medications prescribed (including dose and duration), indication for endoscopy,

Table 1 - Case reports of Whipple's Disease by Brazilian authors

Author	Year	State	Sex	Age	Immunosuppressive factor
Ferrari et al.[4]	2001	SP	M	59	ND
Ferrari et al.[4]	2001	SP	M	20	ND
Ferrari et al.[4]	2001	SP	F	41	ND
Ferrari et al.[4]	2001	SP	M	52	ND
Cabral et al.[5]	2003	SP	M	50	Absent
França et al.[l6]	2004	SP	M	62	ND
Renon et al.[7]	2012	SP	M	61	Absent
Costa et al.[8]	2014	MG	F	57	Absent
Brandes et al.[9]	2015	SC	M	57	Diabetes
Rocha et al.[10]	2015	MG	M	60	Absent
Silva et al.[11]	2017	MG	M	45	Absent
Vaz et al.[12]	2017	SP	M	ND	ND
Vaz et al.[12]	2017	SP	M	ND	ND
Vaz et al.[12]	2017	SP	M	ND	ND
Vaz et al.[12]	2017	SP	M	ND	ND

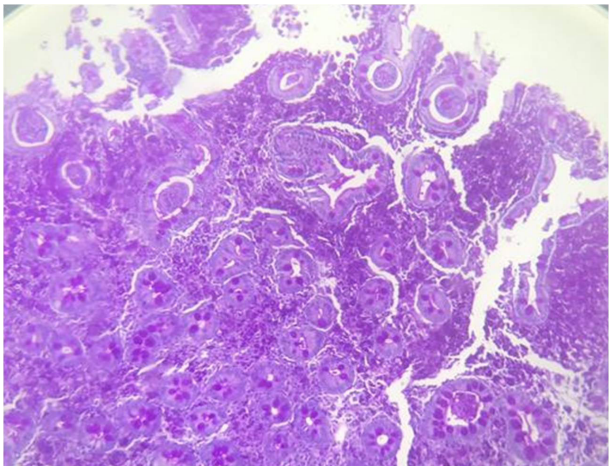
ND= Not Described. Source: Authors.

endoscopic findings, endoscopic photographs of some lesions, histopathology reports, photomicrographs of some lesions, and the results of laboratory and radiographic tests. The diagnosis of WD was based upon histological demonstration of the infection using hematoxylin and eosin (HE) and periodic acid-Schiff (PAS) stains. A minimum of six biopsy specimens were taken from the duodenum on endoscopy. The study was approved for the Ethics Committee (CAAE: 31580620.2.0000.5071).

CASE REPORTS |

In case 1, we have a 48 years old man, baker, Caucasian, Brazilian, From Espírito Santo, Brazil, reporting a 4-month diarrhea liquid and paste (10 times/day) with intermittent blood and hyporexia, nausea, vomiting and weight loss of 20kg. He began to feel pain in small joints of his hands over 06 years ago. There were no neurological changes. He has an alcohol dependence (480g of ethanol/day) and is abstaining for 8 months. On admission the patient was emaciated and pale. The laboratory exams showed iron deficiency anaemia (Hemoglobin: 7,2g/dL, ferritin: 62ng/mL, transferrin saturation: 6% and serum iron: 12ug/dL), hypovitaminosis D [11,7 ng/dL – standard value (SV): greater than 20ng/dL], folate deficiency (2,3 ng/mL; SV= 4 to 20) and hypoalbuminemia (2,8g/dL; SV = 6,4 to 8,3), Anti-HIV, Anti-HCV, HBsAg, antinuclear antibodies and rheumatoid factor negatives. Abdominal ultrasonography showed chronic liver disease, portal hypertension signs, splenomegaly and mild ascites. The esophagogastroduodenoscopy (EGD) detects the presence of esophageal varices and edematous duodenal mucosa with focal erythema and small lymphangiectasias (Figure 1). Duodenal biopsy specimens revealed chronic duodenitis and intracytoplasmic structures in macrophages staining with PAS, suggesting Whipple's Disease (Figure 2). The patient had 2g/day of ceftriaxone, for 14 days, and in 3 days there was an improvement of the diarrhea and arthralgia, and he had more appetite. The patient was discharged prescribed with peroral trimethoprim-sulfamethoxazole (960mg twice daily) for one year. After 7 months of treatment, the patient was asymptomatic, maintaining chronic liver disease at ultrasonography and gained weight (33kg), waiting for a 1-year EGD.

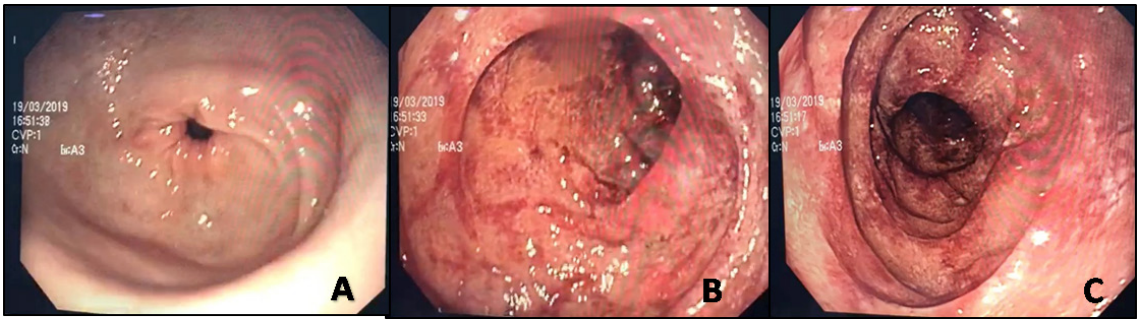
Figure 2 - Whipple´s disease: chronic duodenitis and intracytoplasmic structures in macrophages staining with PAS



Source: Authors.

In case 2, we have a 33 years old man, sewage drainage worker, Caucasian, Brazilian, From Espírito Santo, Brazil. Reporting a 2 years diarrhea liquid and paste and weight loss of 20 kg. He has a history of alcohol dependence. On admission the patient was emaciated and with peripheral edema. There were no neurological and rheumatological changes on physical examination. The laboratory exams

Figure 1 - Macroscopic appearance in EGD of the Whipple's Disease patient: A: normal gastric antrum; B: duodenal bulb; C: second portion of the duodenum; B and C - edema and enanthema, lymphangiectasias and white-yellowish ring-like structures



Source: Authors.

showed leukocytosis (16,600 per mm3; SV = 4,000 – 11,000 per mm3), and hypoalbuminemia (2,6g/dL; SV = 6,4 to 8,3), Anti-HIV, Anti-HCV, HBsAg, HTLV, VDRL and antinuclear antibodies negatives.

Cystoisospora belli oocysts was found in his fecal parasitology. Enlargement mesenteric lymph nodes at abdominal computed tomography. EGD shows enanthematous pangastritis, edematous and wall thickening of the duodenal mucosa. Colonoscopy with nodularity of the terminal ileum mucosa. Duodenal and ileal biopsies specimens revealed chronic inflammation and intracytoplasmic structures in macrophages staining with PAS, suggesting Whipple's Disease. The patient had 2g/day of ceftriaxone, for 14 days with concomitant treatment of the *Cystoisospora belli* with peroral trimethoprim-sulfamethoxazole (960mg twice daily). The patient was discharged prescribed with peroral trimethoprim-sulfamethoxazole and will follow up on ambulatory care.

In case 3, we have a 43 years old man, cleaner, Caucasian, Brazilian, resident of London. Reporting a 4-month abdominal pain, nausea, diarrhea, hematochezia, weight loss, headeache, myalgia and right ankle joint pain. Hepatitis B carrier. He did not show any neurological signs. The laboratory exams showed microcytic hypochromic anemia, Anti-HIV, Anti-HCV, VDRL, HTLV negatives, non-reactive PPD test. HBsAg and anti-HBc positive, Anti-HBs negative. S*trongyloides* stercoralis in his fecal parasitology. Enlargement retroperitoneal and mesenteric lymph nodes at abdominal computed tomography. EGD shows edematous duodenal mucosa and white plaques. Colonoscopy was normal. The duodenal and ileal biopsies specimens revealed chronic duodenitis and intracytoplasmic structures in macrophages staining with PAS, suggesting Whipple's Disease. The patient had 2g/day of ceftriaxone, for 14 days. He had an improvement on the diarrhea and hematochezia. The patient was discharged prescribed with peroral trimethoprim-sulfamethoxazole (960mg twice daily) for one year. The patient returned to London and did not come back to our gastroenterology service.

DISCUSSION |

Whipple's Disease is a chronic infection caused by the bacterium *Tropheryma whipplei*. Human beings are the only known hosts. Saliva and feces from infected patients contain *Tropheryma whipplei*, which contaminate land, clean water, and seawater. Chronic infection occurs when the individual has a genetic predisposition in mutations of HLA alleles, which interfere with the correct presentation of antigens, making *Tropheryma whipplei* remains within the macrophage for years and even decades[3,14].

Despite Whipple's Disease be a rare condition, the infection by *Tropheryma whipplei* seems not to be[7]. PCR of the bacterium are found in 1-11% of healthy individuals, with a higher prevalence in workers who carry out their activities with a higher risk of contamination by pathogens in the stool, such as sewage drainage workers (12 to 26%) and in family members of patients infected with *Tropheryma whipplei* the prevalence was 77% higher than in that of the general population[15,16].

The first symptom of Whipple's Disease in general is arthralgia, characterized by non-destructive migratory extremity arthropathy, which started approximately 6-7 years before the diagnosis, causing an erroneous diagnosis of rheumatological disease. Sometimes, due to confusion, corticotherapy or biological therapy is proposed, which can worsen the disease, progressing to a more severe condition[3,17].

Tropheryma whipplei infection occurs from macrophages, which provides systemic compromise, by the invasion or absorption of bacteria throughout the intestinal epithelium, capillaries, lymph endothelium, liver, brain, heart, lung, synovium, kidneys, marrowbone and skin. The clinical picture can be accompanied by ascites, peripheral edema, steatorrhea, abdominal lymphadenopathy, anaemia, low fever, heart failure, pleural effusion, pulmonary infiltration, lymphomas, and central nervous system impairment, characterized by two pathognomonic neurological signs: oculomasticatory and oculofacioskeletal myorhythmia[3].

The diagnosis of Whipple's Disease is made by finding *Tropheryma whipplei*. Histology of anatomopathological samples of the second duodenal portion, stained by PAS present foamy macrophages with a strong reaction to PAS. It can also be seen, villous atrophy, lymphangiectasis, and large lipid droplets in the lamina propria of the intestinal villi[1]. *Tropheryma whipplei* can also be evidenced by fluid polymerase chain reaction (PCR) or solid tissue immunohistochemistry. Certain diagnosis is considered when two tests are positive[18]. Figure 2 shows the histology of the biopsy of the second duodenal portion, with PAS staining.

EGD of Whipple's Disease patient shows mainly macroscopic changes in the mucosa of the duodenal region, with edema and enanthema from mild to severe, small, and large lymphangiectasias and increased villi, white-yellowish ring-like structures inside of the villi, and milky exudates [19]. Figure 1 shows images taken during EGD.

Several treatments have already been tested. It is currently recommended to start intravenous antibiotic therapy for 14 days with Ceftriaxone 2g / day or Meropenem 1g for 8/8 hours, followed by sulfamethoxazole 800mg + trimethoprim 160mg, orally, twice a day, and duration of at least one year. This treatment may change due to the resistance levels to sulfamethoxazole and the inefficiency of trimetropim[3]. Fenollar, et al., in 2014, reported in France, resistance of *Tropheryma whipplei* of 25.9% to Sulfadiazine in vitro and a good action of doxycycline and hydroxychloroquine, for 12 weeks, in the treatment of the bacteria[14].

Whipple's Disease has high morbidity and mortality and when left untreated has a fatal course. The involvement of the central nervous system can leave the patient with severe impairment due to sequelae or lead to death in 04 years. After treatment with antibiotic therapy, fever and diarrhea improve in a few days and, in weeks, arthralgia improves[3,7].

Follow-up should be performed with a duodenal biopsy at 06 months and 01 year after the start of treatment. If PAS and PCR staining are negative, it is possible to choose to stop antibiotic therapy[3,7]. Some authors recommend keeping a follow-up, with evaluation of PCR in stool and saliva every 2 years[13]. The risk of recurrence in 05 years can reach 33%, with the central nervous system being the main organ affected[20], but is most commonly in the first years, it can occur even after 30 years in patients who are in remission and without treatment [3,15].

CONCLUSION |

The diagnosis of Whipple's Disease remains difficult due to little suspicion of the medical doctors and the disease presents with several nonspecific symptoms. It can take years from the first symptoms to the classic clinical picture. Having knowledge of cases reports helps the doctor to think about the diagnostic probability. In conclusion, starting early treatment on confirmed cases reduces its morbidity and mortality and neurological sequelae.

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