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Whipple's Disease: A Mini Review

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Abstract

Whipple's disease is a rare, multi-systemic chronic infectious disease that preferentially affects middle-aged white men. In 1907 George Whipple first reported it and named this disease "intestinal lipodystrophy". It is a rare condition, estimated incident rate is 1 per 1000000 populations per year. The causative agent is "Tropheryma whipplei". This name originated from Greek word "trophe" (nourishment), "eryma" **(**barrier) and from the name of the person who first reported the disease "George Hoyt Whiplle. It is a systemic disease, mainly affects the gastro intestinal system, and also all the other systems in the body. The classic clinical manifestations are arthralgia, weight loss, diarrhoea, abdominal discomfort, and also include amnesia, dementia, insomnia and dyspnoea. Diagnosis is made generally by small bowel biopsy that reveal characteristic foamy macrophages that are Periodic acid-schiff stain positive. Currently no anystandard treatment regimen approved for Whipple's disease.

Keywords: Whipple's disease, Tropheryma whipplei, intestinal lipodystrophy, Periodic acid- Schiff.

Contents

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1. Introduction

Whipple's disease is a rare, multi-systemic chronic infectious disease that preferentially affects middle-aged white men.[1]In 1907 the first case of Whipple's disease was seen in a 36 year old medical missionary with the symptoms of polyarthritis, dyspnoea, malabsorption, weight loss, and lymphadenopathy. This case was reported by George

Hoyt Whipplei and given the name intestinal lipodystrophy.[2] In 1992 the name for causative agent is suggested as Tropheryma whipplei. After multiple attempts whipplei bacillus was successfully cultivated and stable infected cell lines were established, then the name of causative agent is officially specified as Tropheryma whipplei in 2001. For many years the culture of causative agent has become a mystery for microbiologists. Recent successful isolation and establishment of strains of T. whipplei led to reveal the useful information about the organism characterization, genome sequence, immunologic methods to diagnose the bacterium, and the in vitro organism susceptibility.

Whipple's disease affects multiple systems in the body including central nervous system, gastrointestinal system, cardio vascular system, and joints, of which gastrointestinal system is often most affected.Patients with gastro intestinal symptoms were diagnosed by small bowel biopsy with the help of Periodic acid- Schiff staining. Periodic acid- Schiff staining result is negative for patients with no digestive symptoms. In addition to Periodic acid- Schiff staining, Polymerase Chain Reaction (PCR) is also evolved as a promising method to diagnose the disease.[3] Till now no standard treatment regimen is available, currently accepted therapy is not based on the clinical trials or genomic characteristics of the T. whipplei. Treatment is rather based on case reports and individual patient clinical situation.[4]

2. Epidemiology

Epidemiology of Whipple's disease is still not well documented. Dobbins analysed the epidemiology of Whipple's disease based on observation of 696 cases and from the case reports and case series and reported that Whipple's disease primarily affects men, middle aged adult and whites. A German study showed noteworthy increase in mean age of patients at the time of diagnosis and progressive improvement in female cases.[1,5]

3. Clinical Presentation

The classical clinical symptoms of Whipple's disease are arthralgia, diarrhoea, weight loss, and abdominal discomfort. Polyarthritis is also often reported in some patients. Fever and chills are less common.

3.1. Gastrointestinal symptoms:

The common early manifestations of gastrointestinal system include diarrhoea, weight loss, and abdominal tenderness. Severe symptoms of malabsorpion such as ascites and peripheral oedema are reported in few numbers of cases. Characteristic anatomical abnormalities of the duodenal mucosa associated with lymphectasia are only rarely seen macroscopically during endoscopy.[1,6]

3.2. Central Nervous System:

Whipple's disease mainly affects the central nervous system. Whipple's disease cause neurological manifestations in 10-40% of the patients. The most common central nervous system abnormalities include dementia, loss of consciousness, memory impairment, confusion and altered sleep pattern. Epilepsy, ataxia, seizures, meningoencephalitis are reported in some patients with Whipple's disease. Headache is most frequently occurring symptom. Ocular manifestations such as uveitis, vitritis, retinitis, keratitis, papilloedema have been reported. Eye manifestations are consequence of central nervous system involvement or direct intraocular involvement or both. However no central nervous system manifestations were observed in 50% of the population who were diagnosed with Whipple's disease by Polymerase Chain Reaction analysis of Cerebrospinal Fluid.[1,7-8]

3.3. Joint manifestations:

Most of the people with Whipple's disease were reported with arthralgia, hence diagnosis of rheumatic arthritis is preferred before diagnosing the Whipple's disease. The disease begins gradually with arthropathy. Presence of arthropathy shows HLA-B27positivity, confirming Whipple's disease as a chronic, migratory, and non-destructive, and seronegative joint disease, commonly in the peripheral joints.[1,3,9]

3.4. Other manifestations: Cutaneous findings excluding hyper pigmentation are less common symptoms of Whipple's disease. However subcutaneous nodules are rarely seen in few cases.[1]

4. Bacteriology

The causative agent of Whipple's disease remained unclear for many years. Whipple described that silver stained rod shaped microorganism was seen in the vacuole of macrophages, but he did not correlate this finding with a possible causative organism. In 1960 and 1961 bacteria like agents were noticed by transmission electron microscopy and is strongly suspected that bacteria is a main cause of Whipple's disease. Schoedon and co-workers isolated the causative agent from a heart valve in peripheral blood mononuclear cells attenuated by interleukin 4 and interleukin 10. Furthermore Whipple's bacilli has been isolated and disseminated by injecting in to a human fibroblast cell line with the help of the centrifugation shell vial technique. The causative agent was attained from the heart valve of a patient with T.whipplei stimulated endocarditis and has also obtained from duodenal mucosa, cerebrospinal fluid, and from synovial fluid. The causative agent T.whipplei shows some heterogeneity with a

genome sequence of 16S–23S rDNA interspacer and the 23S rDNA. This organism has a single circular chromosome with a genome size of less than 925kb.[9-10].

5. Diagnosis

Most cases of Whipple's disease involving central nervous system manifestations are not diagnosed until autopsy. Standard diagnostic criteria for diagnosis have not been proposed. The initial diagnostic approach is histological appearance. When the disease is suspected, obtaining a duodenal biopsy is noteworthy.[11] Based on clinical symptoms, reports of additional sample tests such as cerebrospinal fluid, cardiac valve tissue, lymph nodes and synovial tissue should be obtained.

5.1. Laboratory investigations:

No single, specific laboratory abnormality confirms the Whipple's disease. However specific IgG antibodies can be obtained from most of the cases. Although most serum samples show presence of IgG antibodies, however healthy subjects can also develop T.whipplei specific immune response. In comparison with IgG antibodies presence of IgM antibodies looks to be more reliable marker of Whipple's disease.[1] Anaemia is seen in most of the patients. Other laboratory abnormalities include increased erythrocyte sedimentation rate, hypoalbuminemia, and raised C-reactive protein level.[12]

5.2. PCR:

After the successful identification of the nucleoside sequence of causative agent, empowered the improvement of Polymerase Chain Reactionmethod with high sensitivity and specificity. However false positive results might arise from the samples of healthy subjects because of the presence of T.whipplei related microbes in them. Methodological problems such as environmental contamination and difficulties in carrying Polymerase Chain Reaction technique on paraffin sections were noticed.[1,9]

5.3. Periodic acid- Schiff staining:

Endoscopy of the small intestine is still the chief diagnostic measure of choice. Small bowel biopsy reveals characteristic foamy macrophages in lamina propria that are positive on Periodic acid-schiff staining and diastase resistant. Sampling errors might be avoided by taking at least five biopsies from various sites of the duodenum.

5.4. Electron microscopy:

Electron microscopy may helpful for revealing bacterial aetiology however its routine use as a diagnostic method is no longer recommended because it is a complex and time consuming process for standard histological laboratories. However if appropriate specimens are available, additionally electron microscopy could support the diagnosis of Whipple's disease made by other techniques.

5.5. Cultivation:

Cultivation of bacteria in laboratories is quite difficult and is only limited to sophisticated laboratories. It takes several months to cultivate the bacteria, hence it is not the preferred diagnostic technique at the moment.[1]

6. Treatment

If untreated Whipple's disease can be lethal. Treatment for Whipple's disease is based on case reports and retrospective case series, pharmacokinetics of the antibiotics and available preliminary data from in vitro studies.[13]Eradication of the infection and prevent relapses is the primary therapeutic goal in all patients with Whipple' disease. Until the 1950s Whipple's disease was untreatable and many patients lost their life. The first successful treatment for Whipple's disease was achieved by Paulley with the use of chloramphenicol and created a new path in the understanding of aetiology and treatment of Whipple's disease. From the time different types of antibiotics with different schedules were successfully used to treat the disease, and improvement of their clinical status was seen in many patients with the few days of treatment.[5]Until 1980s most of the patients were treated with intravenous penicillin along with streptomycin as a two week course followed by oral tetracycline.[9]

Tetracycline was the first line treatment for many years, but later noticed that relapse rate as high as 35% among tetracycline treated patients, particularly increased chances of central nervous system relapse and low response to further retreatment. A retrospective study with a sample size of 52 patients reported that cotrimoxazloe or a combination of penicillin and streptomycin was effective and no recurrence was found. Moreover a randomized trial in 30 patients with Whipple's disease proved that treatment with cotrimoxazole is superior to tetracycline treatment in patients associated with central nervous system manifestations. Reports of in vitro studies suggest that the organism is susceptible to doxycycline and sulfamethoxazole. Doxycycline in alone possess a bacteriostatic property but in addition with hydroxychloroquine it shows bacteriocidal property. Most authors suggest that the ideal antibiotic in treating Whipple's disease must possess proven effectiveness, less resistance, able to eradicate the organism, and should cross adequately in to the blood brain barrier. Attaining high cerebrospinal fluid levels of antibiotic is much important in treating central nervous system disease. To obtain high cerebrospinal fluid levels, parenteral high dose penicillin, third generation cephalosporins or a carbapenems can be used for the first 14 days as

induction therapy followed by one year continuation therapy with oral cotrimoxazole.[1,5] Supporting the above recommendations, currently most authors suggested that start treatment with parenteral ceftriaxone at a dose of 2 g once daily or meropenem 1g or 2-4 million units of i.v. penicillin G q4h for 2-4 weeks followed by oral cotrimoxazole for one year. Cotrimoxazole can be replaced with oral doxycycline 100 mg twice daily in combination with hydroxychloroquine 200 mg twice a day for one year.[13, 14] A recent in vitro study supports the combination therapy of hydroxychloroquine with oral doxycycline, and recommends that whipple's disease can be managed with combination of doxycycline and hydroxychloroquine for 1 year, followed by doxycycline for the patient's lifetime along with stringent therapeutic drug monitoring.[15] However to prove value of this treatment, efficacy has to be investigated in more number of patients.

6.1. Immune therapy:

Characteristic immunological abnormalities in association with a decreased Th1 response might be seen in patients with Whipple's disease. Hence relapse may occur in some patients. In such cases, treatment with Th1 cytokines such as interferon γ could be helpful as a supportive therapy. However therapy with interferon γ should be initiated only in patients with confirmed relapsing disease and without any inflammatory cerebral lesions. In order to treat with interferon γ, patients with cerebral lesions must be excluded with the help of Magnetic Resonance imaging. This treatment efficacy needs to be proved.[1,3]

6.2. Corticosteroids:

In patients with high central nervous system complications, in association with cerebral lesions and patients those having continuous fever after implementation of antibiotic therapy, adjunctive corticosteroid therapy might be helpful and sometimes lifesaving. Corticosteroids decrease oedema and endothelial damage caused by inflammation.

7. Follow Up

Improvement in clinical status has been seen in many patients after successful initiation of antibiotic therapy. Fever and diarrhoea resolve quickly within one week of start of therapy. Improvement is seen from arthropathy and other manifestations after few weeks of therapy. It takes too long to relieve central nervous system manifestations. Hence follow up of the patients at regular intervals such as at 6^{th} month, 12^{th} month and there after annually is recommended. In patients with gastro intestinal manifestations Polymerase Chain Reaction technique was found to be superior to evaluate the success of the therapy. Polymerase Chain Reaction of cerebrospinal fluid must be performed after 6 months and 36 months [1,9].

8. Conclusion

Whipple's disease is a rare, multi-systemic chronic infectious disease, caused by Tropheryma whipplei. It mainly affects the CNS and GI system. Eradication of the infection and prevent relapses is the primary therapeutic goal in all patients with Whipple' disease. Several combinations of antibiotics were tested regarding their efficacy towards the Whipple's disease. At current most authors suggested that start treatment with parenteral ceftriaxone at a dose of 2 g once daily or meropenem 1g or 2-4 million units of i.v. penicillin G q4h for 2-4 weeks followed by oral cotrimoxazole for one year. However this regimen have shown to be effective in management of Whipple's disease, further studies with the use of other different antibiotics either alone or in combination are needed to provide better treatment to the patients with Whipple's disease.

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