Review

Whipple's disease: a review

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SUMMARY

Whipple's disease was described in 1907 and given the name "intestinal lipodystrophy" until it was found that the agent responsible is a bacterium named Tropheryma whipplei. It's a rare disease which occurs predominantly in males aged 30-60. The small intestinal mucosa is always affected with lesions that are specific to this disease. Replacement of most of cellular elements in the lamina propria by macrophages is characteristic of Whipple's disease. It is a systemic disease that can affect every system, usually causing symptoms in the bowel, the joints, the central nervous and the cardiovascular systems. The diagnosis of Whipple's disease is not easy and depends on a combination of clinical features, the characteristic histopathological findings, the presence of pathognomonic PAS positive macrophages and the PCR of the 16S ribosomal RNA of Tropheryma whipplei. Whipple's disease is lethal if not treated, though it responds dramatically to antibiotic treatment. Patients should be closely monitored during and after treatment because relapses are not uncommon especially when CNS is involved.

Key Words: Whipple's disease, Tropheryma whipplei, treatment

INTRODUCTION

Whipple's disease is a rare systemic infection that affects the small intestine, but it can influence all the organs of the human body. The causative organism is Tropheryma Whipplei (T. whipplei). Its name comes from the greek words "trophe" which means nourishment, "eryma" which means barrier and the name of the man who recognized the first case of the disease "George Hoyt Whipple".[1] The most common symptoms are diarrhea and weight loss, but there are a lot of other manifestations that may not concern the small bowel, like the involvement of mesenteric lymph nodes, athralgias, fever, central nervous system disorders and involvement of the eye.

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HISTORICAL BACKGROUND

Allchin and Hebb reported the first case of Whipple's disease in 1895 without realizing then that it was a special disease. George Hoyt Whipple, in 1907, recognized the first case of the disease that now bears his name. His patient was a 36 year-old doctor, who had gradual weigh loss, indefinite abdominal signs and polyarthritis.[2] His stools consisted of neutral fat and fatty acids. The patient died in approximately five years from the appearance of the symptoms (Whipple 1907). On May 9, 1907 George Hoyt Whipple, then an instructor in Pathology at John Hopkins University performed an autopsy on this patient who had been domiciled at Constantinople (Turkey). The findings at autopsy consisted of polyserositis, aortic valve lesion and deposition of fat within intestinal mucosa and mesenteric lymph nodes with marked infiltration by foamy macrophages.[2] Furthermore Whipple reported the presence of rod-like bacilli approximately 2μm long in the lamina propria of the intestine but he didn't consider that to be the etiology of the disease. Using special stains he noticed the presence of fatty acids but he didn't manage to detect any neutral fat and so he made the mistake of considering this disease to be caused by an abnormality of fat metabolism. Hence he named this disease "intestinal lipodystrophy".[3]

The resemblance between the case of Allchin and Hebb and that of Whipple was found in 1961 when Morgan reviewed the original tissues with stains and demonstrated PAS-positive macrophages. This demon-

stration of PAS-positive macrophages in lamina propria of the small intestine was considered pathognomonic of Whipple's disease. The first report of this disease in a person living was in 1947. In 1952 Pauley was the first to successfully use systemic antibiotics for treatment. In 1958 the first biopsy was performed and it led to the diagnosis of the disease. The turning point in the history of Whipple's disease was the first studies of intestinal mucosa with electron microscopy at the beginning of the 1960's.[4]

The second case of Whipple's disease that was described was in Germany in 1930. As Dobbins reports, 34 cases presented from 1907 to 1950, 245 from 1951 to 1969 and 317 from 1970 to 1984.[4]

Many attempts to cultivate the bacterium have failed. The first successful attempt to cultivate the causative organism was reported in 1997, when human macrophages, inactivated by interleukin 4, were used to grow the bacterium.[5] Another attempt has been made recently, the propagation of T. whipple-coming from an infected heart valve - in human fibroblast cell line.[6] More studies should be made so as to confirm the results.

EPIDEMIOLOGY

The systemic incidence rate is fewer than 18 cases per year (1960) and 30 per year (1980 to 1986) as reported by Dobbins, who analyzed 676 patients.[4] Whipple's disease is a rare bacterial infection. The disease is more frequent among males with a ratio 8:1 according to some statistics. The age range is 35 to 60 years old, but Whipple's disease has been described in infants and in old persons. The reported systemic disease range is 3 months to 81 years (Comer 1983).[7,8] It is interesting that Whipple's disease predominates in white. Caucasians and it may concerns individuals in the same family. It might be associated with immunogenetic factors and a genetic predisposition could be involved.[8] Many patients with Whipple;s disease have a deficiency in the production of interleukin-12 by monocytes macrophages associated with a reduced capability to produce gama interferon by T cells and thus a decreased activation and function of macrophages.[9] In addition HLA B27 is detectable in 28 to 44% of those suffering from the disease while it is found in only approximately 8% of the healthy population.[10,11,12]

Humans are the only known host of the disease. There is no evidence of person to person transmission.[8] In a study Maiwald *et al*. reported the detection of DNA specific for the Whipple's disease bacterium in 25 of 38 wastewater samples from five different sewage treatment plants which was evidence that the environment could be the source of infection with this bacterium.[13] In addition, Whipple's disease was observed with a high frequency in farmers and carpenters, which may also be supportive of the environmental source of the disease.[8] Phylogenetic analysis based on 16rRNA sequence amplification with broad range bacterial PCR primers showed that there is a relationship between T. whipplei and Actinomycetes.[14,15,16]

ETIOLOGY-PATHOGENESIS

Despite the progress that has been made during the last 80 years since the description of Whipple's disease, our knowledge about the etiology and pathogenesis is still not satisfactory. Today it is strongly believed that the causative factor of Whipple's disease is a bacterium.

Since 1961, electron microscopy studies have documented the presence of a bacterium in tissues which were involved, lying free or degraded to varying degrees within macrophages. Whipple's bacillus is a weak gram positive rod shaped bacterium in tissue infected both intracellularly and extracellularly. It is 1.5-2.0 μm in length and has a thick wall, 0.25 μm in width. The inner layer of this wall stains with PAS positive dyes and it is this which is responsible for the brightly staining PAS positive macrophages seen in biopsy tissues. This bacterium is present in a variety of cells, like macrophages, polymorphonuclear leukocytes, mast cells, lymphatic cells, intestinal epithelial cells and smooth muscle cells. Whipple's bacillus was named Tropheryma whipplei. Six genotypes (1-6) of uncultured T. whipplei have been reported based on sequence variation within the inter 16S-23S rDNA spacer and 2 genotypes (named A and B) based on that of the 23S rRNA gene.[17,18,19,20,21]

The PCR testing for bacterial 16S ribosomal RNA (rRNA) genes permitted the specific identification of the presumed causative agent. On the basis of this gene sequence the organism belongs to the gram positive actinomycetes,[22] which are environ-mental organisms, thus, Whipple's bacillus might occur in the environment, as suggested by the presence of T. whipplei DNA in specimens from sewage treatment plants. Based on these an oral transmission of the bacillus can be suspected, which initially colonizes the gastrointestinal system. From there it probably disseminates, via the blood stream and the lymphatic system to other organs.[13] In a prospective study by PCR of gastrointestinal biopsy specimens of 105 patients with no sign of Whipple's disease, positive results were foumd for 11.4% of the gastric fluid specimens and

4.8% of the duodenal biopsy specimens.[22] In addition, in another PCR study, in a random sample of 40 healthy people, 35% were positive for the presence of T. whipplei DNA in their saliva.[23,24] On the basis of the data of these two studies, it is supposed that T. whipplei could be an oral commensal organism and it may be present in healthy individuals without the clinical manifestations. However more studies should be made to confirm the environ-mental source of T. whipplei.

A genetic susceptibility has also been suggested by the observation that approximately 30% of patients are human leukocyte antigen B27 positive.[11]

Strong proof that the rod-shaped bacillus of Whipple is the pathogenic factor of the disease is the clinical improvement of patients after therapy with antibiotics.

HISTOLOGY-PATHOLOGY

Infiltration of organs with foamy PAS-positive macrophages and rod-like bacteria are characteristic of the disease.[25]

The allocation of intestinal lesions varies. They are most serious and common in the duodenum and the jejunum. These lesions may be present in segments which means there is a need to take many specimens for biopsy.[8]

Endoscopy could show normal intestinal mucosa or edematous folds, hemorrhage, yellowish merging plaque. The wall of the small intestine is usually thickened and edematous. According to the description of Whipple, the jejunum is enlarged with red, swollen mucosa without ulceration. The mesentery tends to be markedly thickened and contains numerous enlarged lymph nodes. Jejunal biopsy is the most commonly employed diagnostic procedure.[26,27]

Histological lesions of the disease can be found in different organs. Infiltration of the small intestine is observed in all patients. Section of small intestine reveals large, foamy macrophages within the lamina propria of the small intestinal mucosa. The cell infiltrate distorts the structural pattern of the intestinal villi, thus interfering with nutrient absorption. The lymphatic vessels of the mucosa and submucosa may be dilated and fat droplets are frequently observed in the extracellular spaces of lamina propria. These alterations probably reflect the lymphatic obstruction caused by enlarged lymph nodes and mesentery altered by cell infiltration. These two mechanisms are involved in the genesis of intestinal malabsorption which leads to chronic diarrhea.

Examination with light microscopy shows that the surface of intestinal mucosa is flat without the presence of villi. The sections contain numerous macrophages with large cytoplasmic glycoprotein granules that are PAS positive and resistant to diastase with virtual replacement of most cellular elements by these macrophages. Giemsa, Brown-Hopps-GMS and Warthin Starvy stains reveal no microorganisms. PAS- positive macrophages are found in all affected organs.[25,28,29,30,8]

Electron microscopy, except for all the above findings, shows the presence of small bacilli which are characteristic of the disease. They are in different sites but mainly under the absorptive epithelium and around the vascular system in the upper intestinal mucosa. They are also present in the macrophages. Whipple's bacterium contains an unusual trilaminar plasma membrane, surrounded by a homogenous cell wall, in turn surrounded by a trilaminar membrane structure.[31,32] Therapy with antibiotics shows that there is a rapid disappearance of bacilli from intestinal mucosa and reduction of macrophages. The organs that are affected, apart from the small intestine, are the large intestine, the lymph nodes, the lungs, the heart and the CNS. In these tissues we may have sarcoidlike granulomas as an early manifestation of Whipple's disease, which may mimic those of sarcoidosis, with well formed granulomas and sometimes foreign body giant cells surrounding fat globules.[19,29,33]

CLINICAL FEATURES

Whipple's disease is a systemic disease with a variety of manifestations which depend on the organs or the combination of organs affected. Intestinal manifestations are the most commonly reported and these help to define the "classical" Whipple's disease, but sometimes extraintestinal clinical features, like arthritis, fever and other symptoms often precede for several years. The four most prominent presenting manifestations are diarrhea, weight loss, abdominal pain and migratory athralgia. Less frequent are chills, fever, symptoms from the cardiovascular and the central nervous system (CNS).[34]

The manifestations from the gastrointestinal system are usually the most prominent. These symptoms are chronic diarrhea, abdominal distension, tenderness and those of malabsorption syndrome (abdominal pain, steatorrhea, weight loss). Weight loss and diarrhea are observed less frequently in patients who are diagnosed prior to age 40 and weight loss appears usually to diagnosis. Abdominal pain tends to be epigastric, usually following meals.[35]

At the same time as gastrointestinal symptoms, peripheral swellings appear due to protein loss in the intestine. This loss is huge when the disease affects the mesenteric lymph nodes because of the difficulty in the promotion of various substances and nutrients in the portal system. Acute or chronic bleeding from the intestine may also occur.[36]

Athralgias are transient, migratory, recurrent, grossly symmetric, non-deforming, multiple and may be present intermittently for many years before diagnosis (especially if there is fever). Polyarthritis is usually acute, symmetrical, migratory involving peripheral joints. The knees, ankles, shoulders, wrists and the fingers are the joints most commonly involved. Axial arthritis with sacroiliac and spinal involvement is a rare form of presentation. Vertebral involvement is rare.[37,38,39,40]

Besides the gut, CNS and cardiac findings are the most common. CNS manifestations are confusion, focal cranial nerve signs, memory loss, nystagmus, opthalmoplegia, palpebral ptosis, dementia, insomnia, myoclonus and hypothalamic signs such as hyperphagia and polydipsia. Epilepsy, focal cerebral signs, ataxia and meningitic features may also be present. Headache is a very common symptom, too. Depression, cognitive, decline, confusion, behavioral and personality change and memory loss may progress. Symptoms of the CNS can occur at the time of the initial diagnosis and can accompany intestinal manifestations, but they are more commonly reported as the manifestation of disease relapse during or after antibiotic treatment. In one report 43% had CNS colonization without neurological signs.[41,42,43]

Intraocular manifestations have been reported with or without CNS involvement. Uveitis, retinitis, keratitis, optic neuritis and papilloedema may be found. Other symptoms are non-specific and include glaucoma, chemosis, retinal hemorrhage, fibrovascular pannus, corneal ulcers, optic atrophy and epirhora. Histopathologically PAS positive macrophages have been demonstrated in the eye at autopsy, in vitrectomy specimens, leading to the diagnosis in some patients. Disturbances of ocular movement are the next most common finding. Opthalmoplegia is of supranuclear gaze palsy type with involvement of vertical rather than horizontal movement. Occulomasticatory myorhythmia (OMM) and oculofacial skeletal myorhythmia are said to be pathognomonic for Whipple's disease. OMM is characterized by pendular convergent divergent oscillations of eyes, synchronous with involuntary rhythmic contraction of the muscles of mastication at a rate of approximately one per second.[44,45,46]

Cardiac involvement in Whipple's disease is not uncommon but its clinical occurrence is often overshadowed by gastrointestinal symptoms. There may be involvement of the endocardium, myocardium, pericardium and even coronary arteries. Up to 30% of patients with Whipple's disease have been reported to present with heart murmurs (usually aortic insufficiency, mitral stenosis) and in postmortem studies an even higher incidence of endocarditis is observed.[47]

Other manifestations are skin pigmentation which suggests a severe case of Whipple's disease, peripheral lymphadenopathy, chronic non-productive cough, pleural effusion, pleuritic chest pain and dyspnea.[48,49,50]

Finally, an interesting feature is the differentiation of the clinical course and progress of Whipple's disease, according to Enzinger and Helwing in 3 stages: in the first stage, whose duration could be as many as 20 years, there are non-specific symptoms like athralgias, anorexia, dyspepsia, cough, thoracic pain and low grade fever. The second stage is characterized by consistent diarrhea, abdominal pain, weight loss and the gradual recrudescence of symptoms until the third, final stage which is dominated by the symptoms of malabsorption syndrome and CNS disorders.[51]

INVESTIGATION-DIAGNOSIS-DIFFERENTIAL DIAGNOSIS

Whipple's disease should be suspected in patients with weight loss, diarrhea, athralgias, fever and minor gastrointestinal complaints. It should also be suspected when there is dementia with no apparent cause or chest pain and chronic cough with lung infiltrate which simulates sarcoidosis, skin hyperpigmentation that has no relation to adrenal dysfunction or hyperbilirubinemia.

The physical examination of patients is usually rich in findings that depend on the stage of the disease and mainly on the malabsorption syndrome and the organs that are affected. Low blood pressure, abdominal pain and distention are common findings. Lympadenopathy is present in >50% of patients. The clinical diagnosis may be elusive, especially if gastrointestinal symptoms are not present. The intestinal symptoms are also found in amyloidosis, Crohn's disease and lymphomas. Skin hyperpigmentation is often mistakenly diagnosed as Addison's disease.[8] A unique sign of CNS involvement is oculofacial-skeletal myorhythmia or oculo-masticatory myorhythmia, both diagnostic of Whipple's disease.[46]

Whipple's disease is rare, with many clinical manifestations observed in other diseases, so further laboratory examinations are necesary.

Routine laboratory studies are usually abnormal, depending on the stage of the disease, but they are non-specific. They often include signs of chronic inflammation, like elevated C-reactive protein levels. Anemia, leucocytosis or leucopenia, eosinophilia are also frequently observed. Liver function tests may be influenced. Anemia reflects iron, folic acid or vitamin B12 deficiency. Steatorrhea, reduced xylose absorption and reduction of serum carotene and cholesterol levels are relatively frequent findings.[30]

Radiological examination of the duodenum and other segments of the small intestine shows characteristic pathologic alterations at a rate >85%. The most important findings from this examination are the thickening of duodenal and proximal jejunal folds of mucosa and widening of infected intestine. In a few cases, there is displacement of the stomach and duodenum, possibly due to retroperitoneal lymph nodes.[30]

Brain imaging techniques and electroencephalography show abnormalities which are not pathognomonic. CT and MRI may be normal or show atrophic changes, hydrocephalus and other, but there should also be a differential diagnosis from other diseases such as CNS infection, tuberculosis, encephalopathy, granulomatous disease, AIDS, Alzheimer's disease, Creutzfeld-Jacobs disease. In ECG there is usually slow wave activity.[52,53,54]

When Whipple's disease is suspected, upper gastrointestinal endoscopy is indicated. Esophagogastroduodenoscopy usually reveals thickening of the mucosal folds, the presence of yellow-whitish plaques and erosion. Several biopsy specimens from the lower duodenum should be obtained.[30] Their histopathologic examination usually shows epithelial cells reduced in height-often taking a cuboid conformation-villus atrophy and PAS positive foamy macrophages increased in size throughout the lamina propria. These PAS positive cells are also found in healthy persons and those infected by Mycobacterium avium. The presence of the bacillus is obvious with electron microscopy, which confirms the histopathologic diagnosis, especially in extraintestinal tissues.[30]

The detection of PAS positive macrophages is non-specific. They may also be seen in other gut or lymph node disorders such as histiocytosis, melanosis coli and pneumatoses cystoides intestinalis.[29]

Mycobacterium avium complex infection of the intestine in patients with AIDS may be confused with Whipple disease, although mycobacteria are also Ziehl-Nielsen positive, allowing the differentiation of mycobacterial infection from Whipple's disease.

Infiltration of intestinal mucosa with macrophages is also seen in Histoplasmosis and Macroglobulinaimia but it can be easily diagnosed by experienced pathologists.[54]

Since the recognition of a bacterial etiology in 1961, many attempts have been made to cultivate T.whipplei, but without success. In 1997 Schoeden *et al* reported the propagation of T.whipplei in human macrophages pretreated with interleukin – 4.[5] Recently Rault *et al* reported the propagation of the organism in a human fibroblast cell line and observed a cytopathic effect after 65 days of incubation. This organism had come from an infected heart valve.[6] In 2003 Maiwald *et al* reported the isolation of two new strains of T. whipplei from the cerebrospinal fluid of two patients with intestinal Whipple's disease.[55] This first isolation of T. whipplei clearly shows the presence of bacteria in the CNS in individuals with Whipple's disease. In the above attempts to cultivate the organism, the three main findings that confirm the presence of T. whipplei were: the presence of PAS positive bacilli in an intracellular location in the culture, the amplified sequences of the 16SrRNA gene like those of T. whipplei and the appearance of bacillus with electron microscopy. The recent culture of the organism is a promising project which will allow a new perspective for diagnosis and treatment, but further confirmation with studies is necessary.[56,57]

A standard mean for diagnosing Whipple's disease is the application of PCR assay against T-whipplei. It's a diagnostic tool especially for those with unusual clinical manifestations and laboratory exams. PCR in the bases of sequence analysis of the 16SrRNA gene primers of T.whipplei is useful for monitoring the response to therapy too. The specificity of this examination is one of its important limits. That is firstly because PCR is found positive in persons without clinical symptoms of Whipple's disease. PCR contamination may occur easily if it is correct that T. whipplei is related with environment (commonly found in water). Finally, amplified bands of the presumably appropriate fragment length may be non-specific. Because of the above problems PCR is sometimes used in combination with direct sequencing or hybridization, to confirm the identities of the amplified products. Six different subtypes of T. whipplei have been found by analysis of their 16S-23S rDNA spacer region. Finally interpretation of PCR should be accompanied by histological confirmation and clinical features for a safe diagnosis.[58,59,60]

Serological tests are both useful and important because they can be used to diagnose the disease and the appropriate therapy. There are antigens that can be produced from the cultivation of Whipple's disease bacterium, useful for serological tests. By using a monolayer infected with the bacillus of Whipple's disease an immunofluorescence serological test can be developed. IgG and IgM titers are determined in the serum samples after a special procedure. Many sero-logical studies have shown that the high frequency of IgG antibodies suggest that this pathogen is present everywhere, causing illness only occasionally. This happens perhaps because of differences in virulence among strains or in host factors or because of the presence and correlation of other microorganisms in relation to the immune system. These results need to be confirmed with more studies.[61] The diagnosis of Whipple's disease can also be done by immuno-histochemistry of small intestine biopsy specimens.[62]

THERAPY

The therapy involves the use of antibiotics. To date chloramphenicol, tetracycline, penicillin, streptomycin, TMP-SMX have been used. Other antibiotics used are rifampin and pefloxacin.[63,64] At first Ander's treatment successful with chloramphenicol was largely ignored until the hypothesis of an infectious etiology was confirmed by electron microscopy in 1960, and a series of studies (Trier 1965) proved that antibiotics were the drugs of treatment. In addition the number of deaths and morbidity seem to have decreased with the use of antibiotics.[28]

The most approved therapy is that of Keinath *et al*. after the detailed study of 88 cases with Wipple's disease. So most agree with an initial treatment with 6-24MU IV penicillin G and streptomycin 1gr IM per day for at least 4 days and thereafter TMP-SMX 160-800mg orally 3 times a day for at least one year.[65] Others recommend following on after penicillin/streptomycin with third generation cephalosporine-ceftriaxon- im/iv for at least a month, to be followed by cefixime orally for two years.

Appropriate treatment is used for the complications of the disease such as anticonvulsant drugs for seizures, valproate, clonezepam and piracetam for myoclonus.[66]

Patients should be closely monitored during treatment. The clinical manifestations of Whipple's disease usually improve and PCR becomes negative within a few weeks after the onset of treatment. The histopathological findings may persist for years. Thus the use of PCR is important in evaluating response and adjusting the antibiotic therapy.[67]

Relapse after treatment of Whipple's disease is common and CNS involvement carries the highest relapse rate, which may occur some years after antibiotic treatment is over.[9] In addition, neurological complications are usually more prominent in patients with relapsed Whipple;s disease. Relapse often happens when the initial treatment was of short duration, and relapse is usually more difficult to treat than the initial episode.[68,69]

Whipple's disease, left without treatment, is fatal, but it can be treated nowadays with the use of certain antibiotics. There is, therefore, a need to use every diagnostic means for its diagnosis.

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