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WHIPPLE'S DISEASE: WHAT IS KNOWN AND WHAT IS NEW

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ABSTRACT

Whipple's disease is a rare chronic bacterial infection with a multi systemic pattern, due to Tropheryma whipplei. It occurrs in subjects with cell-mediated immunity defects. It generally begins with a recurrent joint lesion in a middle aged man followed by emaciation and diarrhea diversely associated with other clinical manifestations. The main difficulty is to mention the diagnosis in front of an incomplete or atypical clinical presentation. New diagnostic methods based on immunohistochemistry and genetic amplification by polymerase chain reaction allow making the diagnosis in early stages and in atypical forms of the disease. They permit to prescribe early antibiotic therapy, thereby preventing the development of severe late systemic and sometimes fatal forms of the disease.

KEYWORDS: Whipple's disease; Tropheryma whipplei; Polymerase chain reaction.

INTRODUCTION

Whipple's disease also called intestinal lipophagic granulomatosis or intestinal lipodystrophy or secondary non-tropical sprue is a chronic multi organ bacterial infection caused by the Tropheryma Whipplei bacterium, especially occurring in subjects with deficits in cellular immunity.[1] Since its first description in 1907, many clinical entities related to this bacterium have been reported and which ignorance sometimes led to a misdiagnosis of several years.[2] Recently, Whipple's disease has been the subject of many advances making its diagnosis easier to establish in order to begin treatment rapidly hence avoiding sometimes fatal complications.

BACTERIOLOGICAL AND PHYSIOPATHOLOGICAL RECALL

Tropheryma Whipplei is a telluric germ (wastewater). Its transmission to humans is most probably orofecal or oral route. The inter-human infection has not been reported. Molecular biology techniques have demonstrated the existence of different types of Tropheryma Whipplei infection, responsible for various clinical entities, as well as the existence of healthy carriers.[3]

Immunopathologically, there is a massive infiltration of pathological tissues by macrophages and monocytes containing Tropheryma Whipplei. The replication of this germ in these cells is associated with their apoptosis, thus, leading to its dissemination. On the other hand, this replication is correlated with the expression and release of IL16, which has a high concentration in the disease active phase and is normalized under antibiotic therapy.[4]

Furthermore, other functional and phenotypic abnormalities that persist even after a complete histological remission are in favor of an immune deficiency[1]: decreased lymphocyte response to mitogens, delayed cutaneous hypersensitivity reactions (tuberculin, Candida, dinitrochlorobenzene), intra-mucosal and systemic CD4 / CD8 lymphocyte ratio with increased expression of mature T cell subpopulations and markers of cell activation.[1]

However, the primary or secondary nature of all these abnormalities remains uncertain because these patients don't develop other infections apart from the non-exceptional possibility of giardiasis.[3]

EPIDEMIOLOGY

Whipple's disease especially affects Caucasoid population. According to a recent Italian study[5], its prevalence is estimated at 3 per 1000.000 and seems underestimated because of the ignorance of the disease. Its annual incidence is 1 to 6 new cases per 1000.000 persons.[6] The disease mostly affects the average man, aged 40.[7] Few familial cases have been reported.[7]

ETIO-PATHOGENESIS

Etio-pathogenesis is not yet well understood but seems infectious and immunological.[7] An environmental factor is evoked in front of the common occurrence of this affection in rural environment, especially, among the

farmers.[3] A genetic susceptibility to the disease is not yet demonstrated. The HLA-B27 antigen is reported in 17-28% of cases of Wipple disease with or without axial rheumatic disorder.[8]

Recently, a study of a family composed of 4 members who developed the symptoms of the disease; found that the mutation of the IRF4 gene causes a deficiency of the immune response against the bacteria and would be the cause of the disease.[9] These results deserve to be confirmed by other studies.

CLINICAL EXPRESSION

Apart from asymptomatic carriers, T. Whipplei can be responsible for classic Whipple's disease (characterized by small bowel disease) but also for various localized infections, which are sources of diagnostic errors.[10]

Typically, the clinical signs of Whipple's disease form a triad associating diarrhea, arthralgia and weight loss. Nevertheless, considering its scarcity, slowness of evolution, insidious alternating relapses and remissions as well as its wide range of clinical presentations, its diagnosis is often delayed.

The disease begins most often by articular involvement (67% of cases) or digestive symptoms (15% of cases) or general signs (14% of cases).[10-12]

Whipple's disease usually evolves in two phases: a prodromal phase dominated by arthralgia and a state phase in which the weight loss and diarrhea are the major symptoms.[2]

The average time between the two phases is six years.[2] It can be shortened in immunocompromised patients (under immunosuppressive treatment, corticosteroids, anti-TNF alpha).[10, 11]

Digestive manifestations

Weight loss and chronic diarrhea are part of the classic Wipple disease triad. Weight loss is common and affects 9 out of 10 patients.[1] Diarrhea is often episodic, fluid with sometimes steatorrhea.[3, 11] Other nonspecific disorders such as anorexia, nausea, constipation or meteorism can be seen especially initially.[3] Occult gastrointestinal bleeding, hepatosplenomegaly or ascites have been described.[2] A melena, a polyseritis secondary to hypoalbuminemia as well as an oedematous syndrome are less common.[10, 11]

Usually, in the absence of treatment, Whipple's disease gradually evolves to cachexia in a context of malabsorption then to death.[3]

Note that the digestive signs can be absent throughout the duration of the disease.[1, 10-12]

Rheumatological Presentations

The most common are arthritis (46-61% of cases), however isolated arthralgia are not rare (26-54% of cases).[4, 11-13] Several clinical presentations are possible.

-An intermittent oligo or poly-arthritis, migratory, especially affecting large joints, non-destructive[4,10], can be confused with adult-juvenile rheumatoid arthritis in case of association with a fever with leukocytosis.

-A non-destructive chronic bilateral and symmetrical, non-deforming and sero-negative polyarthritis.[10,13] Subcutaneous nodules have been reported but, unlike rheumatoid nodules, histopathological examination shows foamy macrophages, positive periodic Acid Schiff suggestive of Whipple's disease.[10] Chronic, bilateral, symmetrical and destructive polyarthritis is exceptional which simulating seronegative rheumatoid arthritis.[14]

-Spondylarthropathy

Axial involvement is often associated with peripheral which achieve a spondylarthropathy in 6 to 40% of cases. Radiological exams show unilateral or bilateral sacroiliitis in 14% of cases.[14]

- Others: few cases of Spondylodiscitis, exceptionally inaugural[15], see multistage spondylodiscitis have been reported.[16] Muscular involvement is rare and is mainly manifested by myalgia, amyotrophy[17], dermatomyositis and even orbital myositis.[18] Exceptionally, Whipple's disease is in the hypertrophic osteoarthropathy form.[7]

Neuro-psychiatric manifestations

They are rarely inaugural. Central nervous system involvement is the most serious complication because it is the leading cause of death.[1] These manifestations are various:

- The most frequent one is an alteration of the higher functions (memory disorders, confusion or even dementia irreversible).[2, 3]
- Oculo-masticatory myorhythmias are pathognomonic and occur in one out of five patients: They are continuous rhythmic movements of eye convergence, synchronous with myorhythmias of the muscles of the tongue, palate and mandible and almost always associated with supranuclear oculomotor paralysis.[3]

Others: normal hydrocephalus pressure, myelopathy, hypothalamic syndrome, optic atrophy, cerebellar ataxia, or even cranial nerve involvement.[1] The isolated neurological involvement always affects young people, especially women and its prognosis remains poor.[10]

Psychiatric manifestations such as depression, euphoria, anxiety, psychosis or personality disorders are found in half of the patients.[10, 11]

MRI is used to detect cerebral localizations of Whipple's disease and monitor their progress after treatment.[1] Cerebrospinal fluid (CSF) examination with polymerase

chain reaction and cytological examination involving staining of CSF cells by Periodic Acid Schiff is necessary for diagnosis.[10-12]

Cardiovascular manifestations

Whipple's disease can touch the 3 cardiac tunics

- Pericarditis is found in more than half of cases. It is rarely symptomatic and is unusually constrictive.[10,11]
- Myocarditis is more uncommon and may manifest as rhythm disorder.[11]

Endocarditic preferentially affects the aortic valve, sometimes the mitral valve and rarely the tricuspid valve.[19, 20] As a general rule, the diagnosis of Whipple's disease must be systematically evoked in front of any endocarditis with negative blood cultures.[10, 11, 20]

Other events

- A long-term fever is found in half of the patients and is often moderate, intermittent and accompanied by night sweats.[1] Melanodermia is reported in one third of patients and predominates in areas exposed to light.[3]

-Ocular involvement is observed in more than 10% of cases and is dominated by uveitis.[2] However, keratitis, chorioretinitis and retinal haemorrhages are not uncommon.[1] The diagnosis is often made by Polymerase chain reaction (PCR) on aqueous humor samples.[2]

-Pseudolymphomatous aspects have been described.[2]

-Various pulmonary involvement with cough and chest pain associated with pleurisy, pulmonary infiltrates or mediastinal lymphadenopathy has been reported.[1, 2]

- Finally, orchitis, panniculitis, granulomatous nephritis and amyloidosis have been described.[1, 10]

DIAGNOSIS

The diagnosis is based on both specific and non specific elements.

- **Non-specific elements**

- Inflammatory tests: Inflammatory syndrome of variable intensity, anemia and leukocytosis with neutrophil polynucleosis can be encountered.[10, 11]
- Immunological tests: the search for rheumatoid factor and anti-nuclear antibodies is negative.
- Histopathological examination of biopsied tissues with periodic acid staining of Schiff (PAS) shows a massive tissue infiltrate by foamy macrophages containing gram-positive, PAS-positive and Ziehl-Neelsen negative sickle bodies, called Sieracki corpuscles.[1]

In fact, this positive PAS staining is not pathognomonic because it is found in other infections with intracellular germs, in particular during infections with Mycobacterium Avium[21], Rhodococcusequi[22], HIV, Histoplasmacapsulatum[1], Bacillus Cereus[23] and also in other diseases such as Gaucher disease[1], histiocytosis[24] and Waldenström's macroglobulinemia. Finally, a negative result in the mucosa of the proximal small bowel is an argument against the diagnosis but does not exclude it formally.[3, 10, 11]

-Specific elements

- The gene amplification by the polymerase chain reaction (PCR):

It constitutes the referential examination in the diagnosis of Whipple's disease, especially at the beginning of the disease as well as in atypical forms and / or when the histology proves to be negative[1], and / or when the pathological digestive data are not conclusive.[3]

It can be performed on various tissue samples such as duodenum, lymphadenopathy, synovium, heart valves, kidney, liver, spleen, brain, lungs, muscles and stools.[3, 10, 11]

It can also be performed on a fluid puncture (saliva, joint fluid, aqueous humor or cerebrospinal fluid).[10,11] Its sensitivity and specificity exceed 95%.[1] However, it should be noted that an isolated positive PCR does not support the diagnosis of Whipple's disease because there are authentic false positives.[3] Therefore, to conclude on the positivity of a sample, two PCRs targeting two different DNA sequences must be positive.[1]

- Other means

- Immunohistochemistry uses antibodies against T. Whipplei.[3] It is very sensitive and very specific, allowing to detect the bacteria in the mononucleated cells of many tissues (duodenum, heart valve, lymphadenopathy, ...) or in fluid puncture (blood, joint fluid, aqueous humor ...).[1, 2]
- Electron microscopy is a less available and less sensitive method in comparison with PCR or histological examination.[3]
- Indirect diagnosis through serology is still in the experimental stage and initial results lack sensitivity and specificity.[25-27]

In practice

- Think about a T. Whipplei infection particularly in front of: chronic diarrhea, unexplained prolonged fever, unexplained intermittent arthralgia / arthritis, spondyloarthropathy, uveitis, unexplained neurological manifestations, endocarditis with negative blood cultures, evidence of a non-caseous epithelio-giganto cellular granuloma. The clinical presumption is all the stronger when these manifestations are associated in a middle-aged man.

In case of suspicion of Whipple's disease, saliva and stool samples specific PCR will be performed. If both are positive the positive predictive value is 95.2%, encouraging duodenal biopsy realisation. If both are negative, the negative predictive value is 99.2%. In case of positive salivar PCR, it is a contamination. If PCR is positive in the stool sample, it must be completed by a duodenal biopsy. Positive PAS is in favor of Whipple's

disease. Negative PAS allows the exclusion of Whipple's disease.[10, 28]

TREATMENT AND EVOLUTION

Without treatment, evolution is constantly fatal. The choice of antibiotics must comply with certain criteria, in particular the good intracellular passage, the sensitivity of T. Whipplei and finally the ability to cross the blood-brain barrier (due to the initial risk of asymptomatic damage of the central nervous system and the late cerebral relapses that constitute the seriousness of the disease).[1, 3]

Some authors recommend initial treatment with ceftriaxone (2 grammes per day intravenously) for 2 weeks which will be relayed by trimethoprim-sulfamethoxazole orally (TMP / SMX 160 mg / 800 mg twice daily) for one year.[1, 3, 10-12, 29] Lagier et al.[2] propose to perform at the time of diagnosis, a search for a mutation of the gene folP (gene that codes for dihydropteroatesynthase, the target of sulfonamides) through amplification with gene sequencing.

Under treatment, the evolution is favorable in most cases with disappearance of diarrhea in less than 7 days[10, 11] and improvement of arthralgia from the first 15 days.[2]

Neurological signs persist longer and can last a lifetime. Several cases of relapse (especially neurological) have been described, even after several years of stopping treatment.[2]

Thus, faced with the risks of resistance (30 to 60%) and relapse10 to 35%, the French center of references[10] proposes to treat the classic Whipple's disease and the T. Whipplei infections as follows.

-In the absence of neurological involvement (absence of clinical signs and specific negative PCR in the cerebro-spinal fluid): combination of doxycycline (200 mg / day) and hydroxychloroquine (600 mg / day).

-In case of neurological involvement, in addition to the combination of doxycycline hydroxychloroquine, add sulfamethoxazole-trimethoprim (TMP / SMX 800 mg / 160 mg) 3 times daily, or sulfadiazine 1500 mg / day for at least 18 months. A duodenal biopsy will be systematically performed at the end of the treatment. In case of positivity, the treatment will be continued for 1 year until the next control.

In case of neurological involvement, a cerebrospinal fluid PCR control will be performed annually.[2, 10, 11] The chronic nature of this infection and the risk of relapse require lifelong monitoring.

CONCLUSION

Whipple's disease is a bacterial, systemic pathology that can affect various organs. It is rare and often unknown. The main difficulty is to mention the diagnosis in front of an incomplete or atypical clinical presentation such as diarrhea, arthritis. Genetic amplification by polymerase chain reaction or immunohistochemistry allows making the diagnosis in early stages and in atypical forms of the disease. The institution of early antibiotic therapy avoids systemic complications that are sometimes fatal.

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