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Diagnosis and Treatment of Whipple's Disease

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Contents

Summary 699
1. Epidemiology 700
2. Aetiology and Pathogenesis 700
3. Clinical Characteristics 701
4. Diagnosis 701
   4.1 Differential Diagnosis 702
5. Treatment 702
6. Conclusions 703

Summary

Whipple's disease is a rare systemic infectious disease. To date, it has neither been possible to culture the bacillus *Tropheryma whippelii*, nor to infect other individuals with the pathogen. Today the diagnosis is confirmed by means of polymerase chain reaction (PCR) technology. Typically, the material for the PCR analysis comes from the duodenum. The diagnosis can also be established in this way on the basis of other tissue, or the cerebrospinal fluid.

Treatment should only be carried out with antibiotics which cross into the cerebrospinal fluid, since there can also be an unrecognised involvement of the CNS. At present, the favoured method of treatment is the daily parenteral administration of 1.2 million units of benzylpenicillin (penicillin G) and streptomycin 1g for a period of 2 weeks. This is followed by treatment with cotrimoxazole (trimethoprim 160mg and sulfamethoxazole 800mg) twice daily for 1 to 2 years. The treatment should begin and end with a PCR analysis of cerebrospinal fluid, in order to definitively diagnose infection of the CNS with Whipple's disease and to document the disappearance of the bacillus from the CNS.

A case of Lipodystrophia intestinalis was first reported by Whipple in 1907.[1] The author described the course of the disease now named after him, and documented the significant pathoanatomical changes. He already suspected an infectious disease, but could not provide positive proof. In 1949, Black-Schaffer[2] discovered the positive periodic acid-Schiff (PAS) reaction in the mucosa of the small intestine as an important diagnostic criterion.

In 1952, Paulley[3] reported on the first successful antibiotic treatment of the disease with chloramphenicol; until that time, Whipple's disease had always been fatal. Evidence of a rod-shaped bacil-

lus in the mucosa of the small intestine was obtained by means of the electron microscope in 1961.[4] Until now, it has neither been possible to isolate or culture this bacterium, nor to infect experimental animals. Nonetheless, as a result of examinations of segments of bacteria, it has been found possible to obtain indications of the characteristic features and family of the bacillus by means of polymerase chain reaction (PCR) technology. It has been possible to classify the bacterium responsible for Whipple's disease as belonging to the Actinobacteria family.[5,6] In 1992, it was given the name of *Tropheryma whippelii*.

1. Epidemiology

Whipple's disease is a rare disease. Less than 1000 cases have been reported to date, these being chiefly single-case observations. In postmortem studies, the frequency of the disease is quoted as being less than 0.1%.[7] Men clearly predominate where distribution between the sexes is concerned.[8] All age groups (including children) can contract the disease, although the 40- to 50-year-old age group predominates.[7,9] The disease occurs worldwide; 97% of patients are Caucasian.[9] It appears that a certain genetic disposition is involved. HLA-B-27 is detectable in 28 to 44% of those suffering from the disease, while it is found in only approximately 8% of the average population.[10] There are differing reports on the significance of opportunistic infections. Of late, infections of this type have been reported more frequently.[9,11] Whether the occasionally verifiable immunodeficiency or the macrophage dysfunction are the consequence of the disease or its cause cannot, as yet, be answered definitively.[10,12]

2. Aetiology and Pathogenesis

T. whippelii is a Gram-positive, rod-shaped bacterium, which has been identified both extracellularly and intracellularly. As a result of PCR analysis, the pathogen has been classified as belonging to the Actinobacteria group, which genetically belong to the Actinomycetes. The route of infection is not known with certainty. An oral infectious route of the bacillus is suspected. The bacterium is to be found both in the free lumen of the bowel and in the mucosa. As a postmortem study on 15 patients with Whipple's disease has shown,[7] the small intestine is always infected, with rates in the ileum, jejunum and duodenum being 100, 95 and 58%, respectively. Upon closer examination, the endoscopically extracted duodenal biopsies always show characteristic and, for Whipple's disease, very typical, PAS-positive macrophages. In the majority of cases, these cells are found even if there is an extraintestinal infestation and no reference has been made to abdominal symptoms such as pain or diarrhoea. After antibiotic treatment, the bacilli disappear from the mucosa of the small intestine with varying rapidity; segments of bacteria – corresponding to PAS-positive macrophages – remain detectable in the macrophages for differing periods of time. In case of relapse in which the CNS is affected and which often only becomes apparent after several years, the changes in the small intestine may disappear completely.

When examined under the microscope, the mucosa of the small intestine are oedematous, the intestinal villi are distended and flattened and the lymphatic vessels are dilated. Foamy, changed macrophages are observed, in the cytoplasm of which particles are characteristically stained with PAS reagent. As can be seen with the electron microscope, sections of the bacterial wall are involved. PAS-positive cells are detectable in practically all organs (CNS, suprarenal glands, kidneys, lungs, heart, spleen, pancreas, liver, gall bladder, colon, small intestine, stomach, oesophagus, bone marrow, serous membranes, blood vessels and joints). The disease is almost always identifiable on the basis of mesenteric lymphatic nodes. Epithelial-cell granuloma are often found in the lymphatic tissue.

The inflammatory reaction in the lamina propria of the small intestine (lymphocytes, plasmacytes, eosinophils) is minor, which can be an indication that the bacillus is of low virulence, or that resistance to infection is impaired. The number of these 'inflammatory cells' increases only in long term

infections. As with all chronic inflammations, a secondary amyloidosis (AA-amyloid) is also present in the case of Whipple's disease.[13]

3. Clinical Characteristics

Whipple's disease is an insidious systemic disease. Several organs can be affected without there being characteristic symptoms. As a rule, it can only be diagnosed when diarrhoea occurs and there are signs of malabsorption. The disease begins with nonspecific symptoms such as tiredness, loss of weight, anaemia and arthralgia. The arthralgia takes an intermittent course, and the symptom-free intervals may be long. Several joints are usually affected; most frequently, the lower extremities. In a little less than 20% of cases, a spondylitis is detected, which may be accompanied by sacroiliitis.[12,14,15] Patients often have subfebrile temperatures; an anaemia is normo- to hypochromic and slightly marked. The loss of weight occurs at an early stage. In up to 50% of cases, hyperpigmentation of the skin occurs on areas exposed to light.[10]

With progression of the disease, abdominal complaints such as epigastric pains (which increase postprandially) and diarrhoea are manifested. The stool is fetid and watery; steatorrhoea is present. Due to the malabsorption, there are fat, protein, carbohydrate, vitamin, and mineral deficiencies, together with the known consequences of the deficiency. The further course is characterised by the consequences of malabsorption, as well as by cardiological and neurological deficits. Involvement of the CNS may not be coupled with neurological disturbances, or may be coupled with the widest variety of symptoms (headaches, convulsions, lethargy, visual disturbances, auditory disturbances, gait disturbances, disturbed sleep, impotence or the clinical picture of meningitis).[9,16,17-19] In 80% of cases, cardiac involvement affects the pericardium, in 11% the myocardium and in 53% the endocardium.[12,17] The endocarditis may affect all valves; occasionally, surgical intervention is necessary. If the disease also manifests itself in the eye, which is rarely observed, oedema in the papilla, retinal bleeding, uveitis, corneoretinitis or keratitis occur.[9,10,20]

4. Diagnosis

Although the disease can be identified in the affected tissue and, under certain circumstances, in the cerebrospinal fluid by means of PCR,[18,21] no pathognomic serum test is currently available. We merely find noncharacteristic indications of a chronic inflammation [blood sedimentation rate (BSR), C-reactive protein (CRP), leucocytosis], as well as of malabsorption (deficiency of liposoluble vitamins, hypoalbuminaemia, hypocholesterolaemia, mineral deficiency). Recently, positive PCR proof in the stool of a patient has been reported.[22]

When picture completion tests are used, enlarged retroperitoneal lymphatic nodes are to be seen in 60% of patients.[8,20] Radiological examinations reveal no characteristic changes in the joints. Occasionally, there is a slight demineralisation of the peripheral joints, or a reduction of the joint cavity.

The central computerised tomography (CT) or magnetic resonance imaging (MRI) occasionally reveals cerebral atrophy, hydrocephalus or focal lesions.[23]

In the majority of cases, the disease is definitively identifiable by means of biopsy, taken if possible at the very caudal end of the duodenum. When the mucosa of the small intestine are examined macroscopically, frequently no abnormalities can be detected. Thickened folds, as well as whitish-yellow, confluent patches, are observed in the mucosa. A biopsy in the small intestine is also the correct method when other organs (CNS, joints) are affected.[24] PAS-positive macrophages can be identified histologically. The microscopic changes are often detectable for a long period following antibiotic therapy. The PAS-positive macrophages are also found in other affected organs (lymphatic nodes, cerebrospinal fluid, joint punctate). If identification is not possible by means of cytology or histology, diagnosis can now be made on the basis of the PCR typical of the disease, in the tissue (for

example duodenal biopsy) or puncture fluid (for example cerebrospinal fluid).

4.1 Differential Diagnosis

Where the symptom complex presents as attacks of fever, loss of weight, chronic diarrhoea and arthralgia, Whipple's disease should be considered. In particular, the arthralgia frequently manifests itself much in advance of the other symptoms of the disease. From the point of view of differential diagnosis, other types of infectious arthritis, such as shigellosis, salmonellosis, yersiniosis or campylobacteria infections, or an amoebiasis, should be taken into consideration, as well as Crohn's disease or ulcerative colitis. If the arthralgia predominates, rheumatoid arthritis or immunocomplex disease need to be excluded. Neoplasia, in particular non-Hodgkin's lymphoma, as well as sarcoidosis and immunodeficiency disease, should also be taken into consideration.

Of late, PAS-positive cells which, in the past, were considered to be pathognomic of Whipple's disease, have also been identified in other infections attributable to *Mycobacterium avium intracellulare*, as well as in AIDS.[8] Thus, Whipple's disease should now be confirmed by means of PCR in special cases. Furthermore, morphological similarities have also been identified in macroglobulinaemia Waldenström, disseminated histoplasmosis and *Rhodococcus equii* infections.

5. Treatment

Prior to the use of antibiotics, Whipple's disease had an unfavourable prognosis. Due to the rareness of the disease, no results of large-scale, controlled therapeutic studies are available, so that the recommendations are based on single-case observations.

Although the relationship of *T. whippelii* to the Actinobacteria might be established by means of molecular biology, it has not been possible to culture the bacillus to date. Consequently, tests to determine the resistance to antibiotics are also not currently possible.

In spite of the administration of different antibiotics, including those which cross into the cerebrospinal fluid, the infection of the CNS is still problematical and there are fatal outcomes. No explanation is yet available for this.

Almost all antibiotics have been used in the treatment of Whipple's disease. The first cure was achieved with chloramphenicol.[3] For a long time, tetracycline was used. Only the frequently occurring relapses and the greater awareness of CNS involvement led to a rethinking of antimicrobial strategy. Today, drugs which pass through the blood-brain barrier are used, not only at the commencement of treatment but also in long term therapy.

In a retrospective study of 88 patients, Keinath et al.[25] found relapses in 21 of those affected (35%), occurring on average after 4.2 years (2 months to 20 years). To date, all cardiac and CNS relapses have been observed only late in treatment (after a minimum of 2 years and, on average, after 8.2 years after termination of therapy). 43% of the patients treated solely with oral tetracycline suffered relapses, and 69% of these patients had relapses involving the CNS. In the group described by the same authors, those who primarily received penicillin and streptomycin, and who were treated with orally administered cotrimoxazole (trimethoprim plus sulfamethoxazole) later in the course of their treatment, suffered no CNS relapses.

However, in this context, reports on CNS involvement have also been published in the meantime. Schnider et al.[19] retrospectively collected the treatment strategies employed between 1984 and 1994 in 15 patients with cerebral involvement. In spite of treatment with cotrimoxazole, 3 of 5 patients developed cerebral symptoms. The treatment in these patients, started with a third-generation cephalosporin (ceftriaxone), led to an improvement. One patient who suffered a relapse following ceftriaxone was able to be successfully treated with cefixime.

The recommended treatment[5,10,12,16,17,25-27] at present is daily parenteral administration of streptomycin 1g and benzylpenicillin (penicillin G) 1.2 million units over a period of 14 days, followed by oral cotrimoxazole (trimethoprim/sulfamethoxa-

zole 160mg/800mg) twice daily for 1 year. There are a few alternatives:

1. Cotrimoxazole therapy 3 times daily over a period of 14 days at the above dosage, then twice daily at the same dosage for a further year.[12,28]

2. Initially, parenteral treatment for 14 days with ampicillin 2g three times daily and ceftriaxone 2g daily, followed by twice daily treatment for 1 year with cotrimoxazole (160mg/800mg).[12]

3. Parenteral administration of ceftriaxone 2g twice daily and streptomycin 1g per day for a period of 14 days, followed by cotrimoxazole (at dosage listed above) or cefixime 400mg orally for 1 year.[12]

Under antibiotic treatment, the changes in the mucosa of the small intestine disappear on microscopic examination, on average after 14 months.[23] The PCR test may become negative earlier than this.[20] Some of the individual symptoms improve after a few days; however, it takes on average 7 months for the steatorrhoea to become normalised.[9] Reliable parameters that can indicate the end of the treatment do not exist. Until now, treatment has usually been carried out for 1 year with cotrimoxazole. If there is a supplementary impairment of the immune system, the treatment should be continued for at least 2 years. The patient must be followed up for a minimum of 10 years.

As noted above, relapses occur on average after 4.2 years.[24] In particular, the cerebral relapse manifests itself late and is frequently not associated with intestinal symptoms. As the latest studies show,[17] positive PCR proof in the cerebrospinal fluid is also found with patients who do not, or do not yet, show signs of evidence of cerebral disease. Therefore, our team recommends that the treatment should be started by a cerebrospinal fluid examination, and that the decision to discontinue therapy should only be made when the cerebrospinal fluid produces a negative result in the PCR test.

It remains to be seen whether cerebrospinal fluid diagnosis will be accepted as a treatment criterion. However, it appears to be wise to recommend a procedure of this type.

In the course of therapy, the PAS-positive cells in the duodenum are subject to morphological changes, which can also remain detectable even when the PCR in the duodenal tissue is already negative.[23]

Recently, a report was published on the combination of cotrimoxazole with interferon-γ,[27] which involved a patient with a case of cerebral infection with Whipple's disease which could not be controlled by conventional antibiotics. The patient had evidenced recurrent cerebral symptoms over a period of several years. The combination therapy of cotrimoxazole with interfeeron-γ quickly led to an improvement of the symptoms; after 9 months, the PCR in the duodenum was negative.

6. Conclusions

Whipple's disease is a rare systemic infectious disease. It is frequently accompanied by, in particular, the symptoms of arthralgia, loss of weight, an increased degree of tiredness, anaemia, subfebrile temperatures and chronic diarrhoea. *T. whippelii*, the pathogen, is related to the Actinobacteria. To date, it has neither been possible to culture the bacillus, nor to infect other individuals. Currently, the most certain diagnosis is obtained by means of PCR technology. The PAS-positive macrophages, earlier considered to be pathognomic, are also found in other diseases. Typically, the material for the PCR analysis comes from the duodenum; it is extracted by means of endoscopy. The diagnosis may also be established in this way on the basis of other tissue, or from the cerebrospinal fluid.

Treatment should now be carried out only with antibiotics which cross into the cerebrospinal fluid, since there may also be an unrecognised involvement of the CNS.

At present, the favoured method of treatment is parenteral administration of benzylpenicillin 1.2 million units and streptomycin 1g daily for a period of 2 weeks. This is followed by treatment with cotrimoxazole (trimethoprim 160mg plus sulfamethoxazole 800mg) twice daily for 1 to 2 years. The treatment should begin and end with a PCR

analysis of cerebrospinal fluid, in order to definitively diagnose infection of the CNS with Whipple's disease and to document the disappearance of the bacillus from the CNS.

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