Whipple's Disease

Abstract
Whipple's disease (WD) is a chronic infectious disorder in which almost all organ systems can be invaded by the rod-shaped bacterium – Tropheryma whipplei. Main symptoms are weight loss, polyarthritis, diarrhea/malabsorption, fever and sometimes a complex cerebral manifestation. As WD is frequently misdiagnosed, no reliable data on incidence and prevalence are available. Although WD is susceptible to antimicrobial treatment, no final data from controlled trials are available. Empirical treatment consists of an initial phase of intravenous antibiotics followed by 12 months of antibiotic maintenance therapy. In 1999, a randomised controlled trial on antibiotic treatment of WD has been initiated (SIMW). Patients with untreated Whipple's disease are welcome in the trial: "Third Arm of SIMW".

Keywords
Tropheryma whipplei, Whipple's disease, Morbus Whipple.

Disease and synonyms
Whipple disease, Morbus Whipple
Intestinal lipodystrophy (4)
Intestinal lipophage granulomatosis
Secondary non-tropical sprue

Definition
Whipple's Disease (WD) is a chronic infectious systemic disorder in which all organs can be invaded by the rod-shaped bacterium – Tropheryma whipplei. The main symptoms are weight loss, polyarthritis, diarrhea/malabsorption and sometimes a complex cerebral manifestation.

Differential diagnosis
Seronegative polyarthritis, vasculitis, malabsorption syndrome, endocarditis, cerebrovascular disease, dementia, HIV infection.

Prevalence
As WD is frequently misdiagnosed, no reliable data on incidence and prevalence are available.
Clinical description

Main symptoms of WD are weight loss, non-destructive polyarthritis, diarrhea/malabsorption, fever, lymphadenopathy, cardiac valvular disease, pleuritis and ocular inflammatory disease. Central nervous manifestations consist of the almost pathognomonic triad: dementia, ophthalmoplegia and myoclonus but also of meningoencephalitis with occlusion of the aqueductus and consecutive hydrocephalus, hypothalamic syndromes including disturbance of the sleep cycle, polydipsia and hyponatremia. Untreated WD is characterised by relentless progression and death either by wasting or by central nervous system involvement.

Etiology

*Tropheryma whipplei* (TW), the offending organism has been characterised as an actinomycete. It can be cultivated in human fibroblast cell lines and axenic media (1,2). The findings of *Tropheryma whipplei* in the environment (3) and in healthy persons (8,9), the rareness of the disorder, and the fact that patients affected by WD display an impaired T-cell function (10,11,12) suggest that a specific defect in cellular immunity may be a prerequisite for the infection with *Tropheryma whipplei*.

Diagnostic methods

Because of the protean manifestations of the disease, a high level of suspicion or chance observations are important for early diagnosis. The gold standard for diagnosis of WD is the histological demonstration of the free or phagocytosed rod-shaped bacteria with periodic–acid–SCHIFF (PAS) staining in the duodenal mucosa or other tissue. The diagnosis in extraintestinal tissue has to be supported by a positive PCR (polymerase chain reaction) for *Tropheryma whipplei* (5,6). Cytological demonstration of PAS-positive macrophages or a positive PCR for *Tropheryma whipplei* in the cerebrospinal fluid are diagnostic of cerebral Whipple disease (6,7). As the PCR techniques from different laboratories have not been validated, doubts have been raised concerning the comparability of the results from different laboratories.

As asymptomatic carriers of TW in the gastrointestinal tract have been described, an isolated positive PCR for TW in gastrointestinal mucosa or contents is not sufficient for a definite diagnosis of WD. As PAS-positive macrophages may persist in the intestinal mucosa or frequently in the submucosa for months and perhaps years after successful treatment, the cytological macrophage subtype has to be determined (16).

Management including treatment

Treatment of WD is still empirical as the final results of SIMW are not yet available. Already 50 years ago, it was shown that WD can be cured by antibiotics (13). Antimicrobial treatment may eradicate *Tropheryma whipplei* from the gut, the joints, the heart and lymph nodes whereas central nervous system involvement can persist and can lead to a devastating course some years later (7). The present concept consists of an initial phase of intravenously administered antibiotics known to penetrate the blood-brain barrier followed by 12 months of maintenance treatment (14).

As evidence-based data are not available, any patient with diagnosed WD should be admitted to controlled treatment trials (see below).

Unresolved questions

In vitro microbial susceptibility testing has been performed (17). However, the establishment and maintenance of an in vitro culture is not always possible. Resistance of TW against quinolone antibiotics seems to be a generalised phenomenon (17).

Further, the defect in cellular immunity has not been clearly delineated and it remains an attractive but unproven hypothesis that an impaired T cell function is a prerequisite for the infection with *Tropheryma whipplei*. It can not be excluded that the T cell defect is the consequence of the infection.

Lastly, the natural source of the actinomycete *Tropheryma whipplei* in the environment remains to be studied systematically.

Clinical trials

The recruitment of patients with WD to the SIMW trial (Study for the Initial treatment of Morbus Whipple), initiated 1999, has successfully been terminated in January 2004 after enrolling the predetermined number of 42 patients with untreated WD (15). Final results are not yet available. Follow-up will be complete in 2006. A successor trial based on preliminary results of SIMW with a maintenance treatment period shortened to three months has been established. Trial case report forms and the investigator brochure for the “Third Arm of SIMW” are available in German and English for physicians caring for patients with untreated WD. Patient consent forms are available also in French, Italian, and Flemish (tel. study center: 49 2631 98 1405).

Patients with recurrent disease may be admitted to the Study of Recurrent Morbus Whipple (SRMW).
Research project
A multicenter research project on Whipple's disease is supported by the European Commission (QLG1-CT-2002-01049):
The randomised Study of the Initial treatment of Morbus Whipple (SIMW) is registered by ISRCTN45658456.

Website
www.whipplesdisease.info

References