Whipple's disease

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Abstract

Whipple's disease is a systemic bacterial infection and the common though not invariable manifestations are diarrhoea, weight loss, abdominal pain, and arthralgia. Arthritis or arthralgia may be the only presenting symptom, predating other manifestations by years. Virtually all organs in the body may be affected, with protean clinical manifestations. Various immunological abnormalities, some of which may be epiphenomena, are described. The causative organism is *Tropheryma whippelii*.

The disease is uncommon though lethal if not treated. Recent data suggest the disease occurs in an older age group than previously described. The characteristic histopathological features are found most often in the small intestine. These are variable villous atrophy and distension of the normal villous architecture by an infiltrate of foamy macrophages with a coarsely granular cytoplasm, which stain a brilliant magenta colour with PAS. These pathognomonic PAS positive macrophages may also be present in the peripheral and mesenteric lymph nodes and various other organs. The histological differential diagnoses include histoplasmosis and *Mycobacterium avium–intercellulare* complex.

The clinical diagnosis of Whipple's disease may be elusive, especially if gastrointestinal symptoms are not present. A unique sign of CNS involvement, if present, is oculofacial-skeletal myorhythmia or oculomasticatory myorhythmia, both diagnostic of Whipple's disease. A small bowel biopsy is often diagnostic, though in about 30% of patients no abnormality is present. In patients with only CNS involvement, a stereotactic brain biopsy can be done under local anaesthetic. A recent important diagnostic test is polymerase chain reaction of the 16S ribosomal RNA of *Tropheryma whippelii*.

Whipple's disease is potentially fatal but responds dramatically to antibiotic treatment. In this review the current recommended treatments are presented. The response to treatment should be monitored closely, as relapses are common. CNS involvement requires more vigorous treatment because there is a high rate of recurrence after apparently successful treatment.

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The first case of what is now termed Whipple's disease was reported by Allchin and Hebb in 1895.[1] In 1907 George Hoyt Whipple, the first American Nobel Laureate in physiology, described a 36 year old medical missionary with transient polyarthritis, fever, tiredness, and weight loss who then developed diarrhoea.[2] Whipple attributed the illness to intestinal lipodystrophy caused by abnormal fat metabolism. The work of Paulley[3] in England established the critical relation between antibiotic treatment and disease remission, and in 1961 "bacillary bodies" highly suggestive of an infectious agent were described.[4 5]

Wilson's group elaborated on the infective agent of Whipple's disease, using nucleotide sequencing and amplification by reverse transcriptase polymerase chain reaction (PCR) of bacterial 16S ribosomal RNA from the small intestinal biopsy of a patient with Whipple's disease.[6] They identified a previously unknown organism related genetically to *Rhodococcus*, *Streptomyces*, *Arthrobacter*, and more weakly to *Mycobacter* species. Owing to the lack of similarity to any known genus and based on DNA sequencing and phylogenetic relations and its distinct morphology, the bacillus was assigned by Relman *et al* (1992) to a new genus and species and termed *Tropheryma whippelii*,[7] from the Greek words *trophe* (nourishment) and *eryma* (barrier), and George Whipple's surname. The organism is Gram positive, periodic acid Schiff (PAS) positive, and diastase resistant.[7]

Whipple's disease can now be described as a systemic bacterial infection caused by *T whippelii*, with diarrhoea, weight loss, abdominal pain, and arthralgia as the most common though not invariable manifestations.[8–10]

Epidemiology

It is estimated that Whipple's disease has occurred in 1500–2000 patients,[11] predominantly in middle aged white males.[12] More recent data identify a somewhat older age group: in 52 patients with Whipple's disease the mean age at diagnosis was 55 years and the age range 20–82 years.[13] Whipple's disease has been reported in siblings.[13–15]

Pathology

The pathological features of Whipple's disease are summarised in box 1. The characteristic pathological changes occur in the small intestine, especially the jejunum. Macroscopically the small bowel is dilated, thickened, and rigid, with a fibrinous exudate on the peritoneal surface.[16] The mesenteric (and para-aortic) lymph nodes are enlarged.[17]

The microscopic features are distension of the normal villous architecture by an infiltrate of foamy macrophages which replaces the

Box 1: Pathological changes in the small intestine

Macroscopic
- Dilated, thickened and rigid intestine
- Fibrinous exudate on the peritoneal surface
- Enlarged mesenteric lymph nodes

Microscopic
- Villi distended by an infiltrate of foamy macrophages
- PAS positive macrophages with coarsely granular cytoplasm
- Variable villous atrophy
- "Intestinal lipodystrophy"

lamina propria and often extends into the muscularis mucosa or submucosa. These macrophages, with a coarsely granular cytoplasm, stain a brilliant magenta colour with PAS. The characteristic cytoplasmic granules are clumps of *T whippelii* (approximately 2 μm in length and 0.2 μm in diameter) and their degradation products. These pathognomonic PAS positive macrophages may also be present in the peripheral and mesenteric lymph nodes, liver, spleen, heart valves, brain, and lungs,[18–21] eye and spinal cord,[22] and occasionally in the synovium.[23]

Another characteristic feature in small bowel biopsies is rounded empty spaces scattered through the lamina propria which contain neutral fat, described as intestinal lipodystrophy by Whipple in 1907.[2] A marked inflammatory response is absent despite the infective nature of the disease. In a minority of patients non-caseating granulomas are present in the intestine, mesenteric and peripheral lymph nodes, liver, lungs, brain, and meninges. The histological differential diagnosis includes histoplasmosis and *Mycobacterium avium–intercellulare* complex (MAIC).

Clinical features

PRESENTING FEATURES

Whipple's disease is a serious pervasive illness. As all organ systems in the body may be affected the clinical features are extensive and varied. The most frequent and predominant manifestations result from small intestinal involvement.[11] The combination of weight loss, diarrhoea, and polyarthralgia is a common presenting symptom complex. Whipple's disease may manifest itself for many years only as a low grade fever in about half the patients.[24] Peripheral lymphadenopathy occurs in up to 50% of cases.[25] The musculoskeletal, cardiovascular, and central nervous systems (CNS) are often involved; the presenting or most severe features of the illness may be non-gastrointestinal. Rarely the presentation may be neurological[26] or ophthalmological.[27]

GASTROINTESTINAL TRACT

Whipple's disease most often involves the gastrointestinal tract, resulting in weight loss, diarrhoea from malabsorption (the commonest symptom), and less often abdominal pain.[13 14] Fat malabsorption (steatorrhoea) results in stools that are bulky, greasy, foul smelling, difficult to flush away, and leave a film of oil in the toilet pan after flushing. Protein and vitamin malabsorption may lead to oedema and ascites, anaemia from iron and folate malabsorption, bleeding and clotting disorders from vitamin K deficiency, and rarely osteopenia from a deficiency of vitamin D. Small bowel involvement is not invariable[9] or may be patchy, and malabsorption and diarrhoea may be inconsequential.[28–30] Though unusual, bleeding from the gastrointestinal tract, both occult and gross, is reported.[15 31 32]

Abdominal pain may occur in the epigastric area after food, mimicking peptic ulcer or gall bladder disease. Other symptoms are anorexia and flatulence. Abdominal palpation may reveal a mass caused by lymph node involvement, splenomegaly, or distended loops of intestine. Peritonitis may be a feature.

Box 2: Common presenting clinical features

- Weight loss
- Diarrhoea
- Polyarthralgia
- Low grade fever
- Peripheral lymphadenopathy

MUSCULOSKELETAL SYSTEM

In 67% of patients arthralgia or arthritis are the only symptoms,[13] and may predate other manifestations by years.[33] The polyarthritis is mild, migratory, and episodic and lasts for a few days to a few weeks, followed by long periods of remission. Neither chronicity nor permanent joint damage or deformity is a feature.[13 34] The limb and girdle joints are most often affected.[13] In Durand's series,[13] peripheral joint involvement occurred in 35 of 52 patients (67%); in five patients with back pain there was no radiological evidence of spinal lesions. Ankylosing spondylitis is rare.[35] The prevalence of HLA-B27 is 8–33% in patients with axial arthritis.[35] A myopathy has been described in a small number of patients.[36 37]

CARDIOVASCULAR SYSTEM

Cardiac involvement was the initial presentation in 11 of 19 patients (58%) and at necropsy adhesive pericarditis, myocardial fibrosis, and valvar deformity was present in 15 (79%).[20] Low blood pressure, myocarditis, and pericarditis are reported.[13 38 39] Endocarditis of the mitral valve as in rheumatic valvar disease is common.[13 38]

CENTRAL NERVOUS SYSTEM

In Whipple's disease, CNS manifestations occur in 10–50% of patients.[13 15 40 41] However, despite the absence of neurological signs and symptoms, on necropsy brain involvement is often documented.[42] The clinical features of

CNS involvement may be the only presentation.[13 22 26] The occurrence of CNS features may postdate, by years, the development of gastrointestinal symptoms.[43] The reason for the predilection of the organism to the CNS is not known.

The clinical features of CNS disease are diverse, as Whipple's disease may affect the brain stem, the diencephalon (epithalamus, subthalamus, and hypothalamus), the rhinencephalon (that part of the cerebral hemisphere directly related to the sense of smell), the medial temporal lobe,[9] and the meninges.[13 42] Confusional states, coma, and brain stem syndromes, seizures, cerebellar ataxia, and myelopathy are common features.[13 15 44 45] Cognitive changes were reported in 71% of 84 patients, and of these psychiatric problems occurred in 47%.[40] Dementia, supranuclear ophthalmoplegia, and myoclonia are the three most commonly observed symptoms, occurring in 25–50% of patients.[13 15] Hearing loss and vestibulo-ocular reflex impairment are associated with peripheral labyrinthine or cranial nerve involvement.[41]

Involvement of the hypothalamic-pituitary axis results in polyuria and polydipsia.[15] Other prominent clinical features are hypogonadism, hyperphagia, weight gain, insomnia, and hypersomnia, which may be a prominent feature.[46–48] Though no specific study on the extent of dementia in Whipple's disease is available, this problem is often mentioned in case histories of patients.[22 26 40 46 49] In large series, 20–50% of patients with CNS involvement have been reported as having dementia.[13 15] Of particular interest are two patients with Whipple's disease reported by Durand *et al* in 1997, aged 65 and 54 years, with "predementia state" and dementia.[13] In the patient with "predementia," despite the absence of gastrointestinal symptoms, markers of inflammation prompted a small intestinal biopsy which confirmed Whipple's disease. The second patient declined investigations but accepted treatment with trimethoprim-sulphamethoxazole, whereupon diarrhoea and dementia of three years' duration resolved.

Oculomasticatory myorhythmia (OMM) is a unique finding in Whipple's disease, characterised by a slow, smooth convergent–divergent pendular nystagmus associated with synchronous contractions of the jaw.[9 46 50 51] Oculofacial-skeletal myorhythmia has also been described: a slow smooth convergent–divergent pendular nystagmus associated with synchronous contractions of other body parts.[52–54] These signs occur in 20% of patients with CNS disease and are always associated with a supranuclear vertical gaze palsy.[40] Both signs are rare but pathognomonic of Whipple's disease,[26 46] and are of equal diagnostic value to a positive biopsy or positive PCR assay for the bacterial RNA.[9]

Ocular involvement

The only presentation may be ophthalmological.[27] Ocular manifestations of Whipple's disease result either from CNS involvement, or from specific intraocular pathology, or both. Uveitis and ophthalmoplegia are common findings in patients with Whipple's disease.[27 55] In a series of 34 patients with ocular manifestations the cause was solely intraocular in only four, as opposed to a CNS cause in the remaining 30.[55] The ocular abnormalities include supranuclear ophthalmoplegia,[13 15] uveitis, ophthalmoplegia and diffuse chorioretinal inflammation,[27 55] glaucoma, epiphora, superficial punctate keratitis, and an unusual pannus involving the anterior chamber angles and corneal periphery of both eyes.[56]

Meningeal involvement

Though uncommon, Whipple's disease can cause chronic and recurrent meningitis.[57] PAS positive macrophages are present in the biopsies of the meninges.

SKIN

In about 50% of patients a generalised hyperpigmentation occurs, most often in exposed areas, but not in the buccal mucosa as in Addison's disease. Subcutaneous nodules that resemble rheumatoid nodules are described, and on biopsy may show the diagnostic features of Whipple's disease.[13] Other skin manifestations are purpuric lesions not due to thrombocytopenia.

HAEMOPOIETIC SYSTEM

Mesenteric, retroperitoneal, mediastinal, and peripheral lymphadenopathy is reported.[13 25] Haematological abnormalities include anaemia, a common finding resulting primarily from iron deficiency but less often from folate deficiency, and disorders of bleeding and clotting, associated with vitamin and mineral malabsorption.

RESPIRATORY SYSTEM

A chronic cough and pleural pain associated with pleural effusions, hilar lymphadenopathy, and pulmonary infiltrates are respiratory manifestations.[13 24] Radiological findings include nodular shadows and parenchymal bibasal interstitial infiltrates.[25] In patients with a chronic cough, pleural involvement has been reported in 72% on necropsy.[13]

IMMUNE SYSTEM

Abnormalities of immune function in patients with Whipple's disease may predispose to infection with *T whippelii*.[58–61] An in vitro defect in the intracellular killing function of monocytes and macrophages persists, even in remission.[58 60 61] A primary defect in monocyte production of interleukin-12 reduces γ interferon production by T lymphocytes.[62] Other immunological abnormalities include suppressed delayed type hypersensitivity responses in vivo, decreased in vitro T cell responses, and altered lymphocyte subpopulations.[63]

However, some immune abnormalities may be epiphenomena of disease. Major histocompatibility complex (MHC) class II antigens are constitutively expressed on small intestinal enterocytes. In 20 patients with Whipple's disease, MHC class II antigen expression was reduced or absent, but restored after treat-

Questions on Whipple's disease

- What are the most frequent presenting symptoms of Whipple's disease?
- Although the clinical features of CNS involvement in Whipple's disease are diverse, what are three of the most commonly observed symptoms?
- What clinical symptoms, although rare, are pathognomonic of Whipple's disease and considered to be of equal diagnostic value to a positive biopsy or positive PCR assay for the bacterial RNA?
- What are the characteristic small bowel biopsy features?
- What treatment would you recommend for a middle aged patient newly presenting with biopsy confirmed Whipple's disease?
- What tests help in the diagnosis of Whipple's disease?

ment.[59] This reduction in MHC class II antigen expression is attributed to a deficiency in the inflammatory or immune response and not to damage to intestinal epithelial cells. Dobbins has noted that "the Whipple bacillus has an unusual ability to enter cells and the mucosa while failing to provoke injury or an intense immune reaction."[15] IgA-bearing plasma cells in the intraepithelial lymphocyte subpopulation of the small intestine are also destroyed in Whipple's disease, but return to normal after treatment.[64]

The diagnosis

The clinical diagnosis of Whipple's disease at the onset of the illness may not be easy. The symptoms are protean, sometimes non-specific, and involve many organ systems. The occasional absence of symptoms related to the gastrointestinal tract may compound the diagnostic problem.[10 26 27] It has been suggested that, clinically, oculofacial-skeletal myorhythmia or oculomasticatory myorhythmia alone establishes the diagnosis of Whipple's disease.[9]

Early diagnosis is essential. Whipple's disease is potentially fatal but responds dramatically to antibiotic treatment. In the past the diagnosis was established by the characteristic findings in a small intestinal biopsy. However, the small bowel biopsy was not diagnostic in about 30% of cases.[40] Histological examination continues to be a common diagnostic procedure on small bowel biopsy, now conveniently obtained by endoscopy.[65 66] It is important that *Mycobacterium avium* is excluded by acid-fast staining.

The erythrocyte sedimentation rate (ESR) is invariably raised at the time of diagnosis. Haematological and biochemical abnormalities may be present. As the gastrointestinal tract lesion in Whipple's disease is primarily in the upper small intestine, iron and folate concentrations may be decreased, though vitamin B-12 concentrations are rarely abnormal as the terminal ileum is not usually affected. Severe hypoproteinaemia is common and tests of malabsorption, such as the d-xylose absorption test and three day faecal fat excretion, are abnormal if the small bowel is involved. These tests may now be unnecessary to establish malabsorption resulting from small bowel pathology, as an endoscopic biopsy can provide the same information. On endoscopy, the findings in 12 patients were: oesophagitis (1), erosive gastritis (4), atrophic gastritis (2), severe erosive bulbitis (3), and pathognomonic postbulbar duodenal lesions (9), and after antibiotic treatment these lesions resolved in 20% within six months, and in all the patients by nine months.[66] However, PAS positive macrophages can persist in endoscopic biopsies for years.[13 66] Though histological examination of the small bowel continues to be a popular diagnostic test, in about 30% of patients with Whipple's disease no abnormality is found.[40]

Radiology of the small intestine shows thickening of mucosal folds and other features typical of malabsorption, depending on the severity of the lesion. Computed tomography or magnetic resonance imaging of the head shows localised lesions and also serves to monitor resolution with treatment.[26 41] In Whipple's disease of the CNS, the diagnosis can be established by stereotactic brain biopsy under local anaesthetic, a procedure that is minimally invasive.[26] If there is skeletal involvement, radiology of the hand may show changes, as in rheumatoid arthritis, and there may be ankylosing spondylitis in the sacroiliac joint.[67] Synovial biopsy and synovial fluid examination show mild non-specific inflammatory changes. Rheumatoid factor and antinuclear antibodies are absent.

Current effective diagnostic tests are based on nucleotide sequencing and amplification by reverse transcriptase PCR of bacterial 16S ribosomal RNA from biopsy samples. This test uses specific primers unique to the ribosomal RNA of *T whippelii* to search for matching RNA sequences. Successful amplification of a DNA product of the expected size and sequence from tissue samples confirms the presence of *T whippelii* 16S ribosomal gene sequences. A negative result in the absence of the organism reflects the rigid conditions of the PCR test, which only allows amplification of genetic material with a very close match to the specific primer. PCR testing is also a valuable tool to monitor disease progress and forestall relapses.

The PCR test was positive in intestinal biopsy samples from all 30 patients with Whipple's disease in one study,[68] and in another study it was positive in 29 of 30 patients with histological evidence of Whipple's disease.[10] A German study found samples from eight patients with Whipple's disease positive for PCR, but none of 54 tissue samples from 34 controls.[69]

However, the current PCR assay may not be specific enough.[70] The PCR test was positive despite there being no evidence of Whipple's disease in 14 of 105 subjects referred for elective gastroscopy. This suggests that *T whippelii* or a closely related organism may

Box 3: Multisystem features of Whipple's disease

Gastrointestinal involvement:
- Weight loss
- Diarrhoea
- Abdominal pain
- Malabsorption: oedema, ascites, mineral and vitamin deficiencies

Musculoskeletal involvement:
- Polyarthralgia

Cardiac involvement:
- Pericarditis
- Myocardial fibrosis
- Valvar deformity

CNS involvement:
- Confusional states
- Cognitive changes
- Oculomasticatory myorhythmia
- Oculo-facial-skeletal myorhythmia
- Myelopathy

Ocular involvement:
- Uveitis
- Ophthalmoplegia

Skin involvement:
- Skin hyperpigmentation
- Subcutaneous nodules
- Purpuric lesions

Respiratory involvement:
- Chronic cough
- Pleural effusions
- Pulmonary infiltrates
- Hilar lymphadenopathy

Box 4: Treatment regimens for Whipple's disease (adapted from Singer 1998 [76])

Regimen 1:
Once daily parenteral administration of:
Benzylpenicillin (penicillin G) 1.2 MU plus streptomycin 1 g for 14 days,
Followed by oral trimethoprim-sulphamethoxazole (TMP-SMX) (160+800 mg) twice daily for 1–2 years

Regimen 2:
Oral TMP-SMX (160+800 mg) ×3/day for 14 days,
Followed by oral TMP-SMX (160+800 mg) twice daily for 1–2 years

Regimen 3:
Ceftriaxone 2 g parenterally ×3/day plus ampicillin 2 g parenterally ×3/day for 14 days,
Followed by oral TMP-SMX (160+800 mg) twice daily for 1–2 years

Regimen 4:
Ceftriaxone 2g parenterally twice daily plus streptomycin 1 g/day for 14 days,
Followed by oral TMP-SMX (160+800 mg) twice daily for 1–2 years

OR:
Oral cefixime 400 mg daily for 1–2 years

be present in "normal" people; host or bacterial factors may prevent the development of Whipple's disease.[70]

A new PCR assay is being developed to avoid cross reaction between genetic material from closely related species.[71] Other recent developments in the diagnosis of Whipple's disease include less invasive tests, for example using peripheral blood[72] and samples of faeces.[73]

Management

The life saving value of antibiotic treatment in Whipple's disease was established in 1952.[2] The current recommended treatment for Whipple's disease is long term trimethoprim-sulphamethoxazole, as it crosses the blood–brain barrier.[74–76] Folate supplementation is advisable, because trimethoprim-sulphamethoxazole may cause folate malabsorption. Dramatic symptomatic relief of gastrointestinal and musculoskeletal symptoms may occur in days. Histological improvement of the small bowel mucosa takes place rapidly,[8 65 77] but total histological remission may require about two years or longer.[33 58] The radiological changes of bone involvement may need six to nine years to resolve.[78]

When CNS involvement occurs, treatment should be more vigorous, with antibiotics that cross the blood–brain barrier. CNS symptoms have a high rate of recurrence after apparently successful treatment.[15 79] Schnider *et al* recommend initial treatment with intravenous ceftriaxone, 2 g twice daily, plus streptomycin, 1 g once daily for two weeks, or a one to two week course of intravenous trimethoprim-sulphamethoxazole, 960 mg twice daily. Treatment should then be continued for one year with oral trimethoprim-sulphamethoxazole (co-trimoxazole), 960 mg twice daily, or oral cefixime, 400 mg once daily.[75]

Singer[76] recommends that Whipple's disease be treated with the parenteral administration of streptomycin 1g a day and benzyl penicillin (penicillin G) 1.2 million units a day for two weeks, followed by twice daily oral doses of 960 mg of trimethoprim-sulphamethoxazole for one year, or at least two years if there is a "supplementary impairment" of the immune system, with monitoring of the patient for a minimum of 10 years. There are several alternative treatments, set out in box 4.[76]

A potential new treatment with γ interferon 150 μg three times a week with concurrent trimethoprim-sulphamethoxazole twice daily for 16 months was effective in a 66 year old patient with cerebral Whipple's disease which could not be controlled by a variety of conventional antibiotics over a period of 10 years.[80]

The response to treatment has been monitored by the clinical improvement and the absence of *T whippelii* on histological examination. The usefulness of PCR for monitoring the response to treatment has been reported.[10 76] This approach is particularly valuable, as the relapse rate is high in Whipple's disease even

Answers to the questions:

- The most frequent and dominant manifestations are caused by small bowel involvement and the consequences of malabsorption. The combination of weight loss, diarrhoea, and polyarthralgia is a common presenting symptom complex. Whipple's disease may manifest itself for many years only as a low grade fever in about 50% of patients. Peripheral lymphadenopathy occurs in up to 50% of cases. In 67% of patients, arthralgia and/or arthritis are the only symptoms and may predate other manifestations by years.
- Dementia, supranuclear ophthalmoplegia, and myoclonia are the three most commonly observed symptoms, occurring in 25–50% of patients. Cognitive changes were reported in 71% of 84 patients.
- Oculofacial-skeletal myorhythmia and oculomasticatory myorhythmia are both diagnostic of Whipple's disease. These signs occur in 20% of patients with CNS disease and are always associated with a supranuclear vertical gaze palsy.
- Characteristic microscopic features are distension of the normal villous architecture by an infiltrate of foamy macrophages which replaces the lamina propria and often extends into the muscularis mucosa or submucosa. These macrophages have a coarsely granular cytoplasm and stain a brilliant magenta colour with PAS. The characteristic cytoplasmic granules are clumps of *Tropheryma whippelii* and their degradation products. Another feature is rounded empty spaces scattered through the lamina propria that contain neutral fat, described as intestinal lipodystrophy by Whipple in 1907.
- The most commonly recommended regimens use antibiotics that cross the blood–brain barrier, usually treatment with oral trimethoprim-sulfamethoxazole (co-trimoxazole) 960 mg twice daily for one year, often following initial treatment with intravenous antibiotics for two weeks. See box 4 for a summary of recommended treatments.
- (A) Small bowel biopsy; (B) PCR assay for *Tropheryma whippelii* RNA.

after apparently successful treatment.[33 66 81] Treatment should begin and end with a PCR analysis of cerebrospinal fluid in order to make a definitive diagnosis of infection of the CNS and to document the disappearance of the bacillus.[76 82] Relapse is defined on the basis of morphology (preferably) or clinically, or both, as recommended by Keinath *et al*.[74] In a series of 88 patients, 35% experienced relapses.[74] Many relapses take the form of cerebral involvement[44] and are caused by treatment with antibiotics that have not crossed the blood–brain barrier. This high rate of recurrence occurs when only tetracycline or penicillin, alone or in combination, are used.

Whipple's disease is an important condition to diagnose as it responds dramatically to treatment. The complex clinical picture requires a high degree of suspicion. The goals of management should be vigorous treatment and continuous vigilance with regard to possible relapse.

1 Morgan AD. The first recorded case of Whipple's disease. *Gut* 1961;**2**:370–2.
2 Whipple GH. A hitherto undescribed disease characterised anatomically by deposits of fats and fatty acids in the intestinal mesenteric lymphatic tissues. *Johns Hopkins Hosp Bull* 1907;**17**:382–91.
3 Paulley JW. A case of Whipple's disease (intestinal lipodystrophy). *Gastroenterology* 1952;**22**:128–33.
4 Yardley JH, Hendrix TR. Combined electron and light microscopy in Whipple's diseasedemonstration of "bacillary bodies" in the intestine. *Bull Johns Hopkins Hosp* 1961;**109**: 80–98.
5 Chears WC, Ashworth CT. Electron microscopic study of the intestinal mucosa in Whipple's disease. Demonstration of encapsulated bacilliform bodies in the lesion. *Gastroenterology* 1961;**41**:129–38.
6 Wilson KH, Blitchington R, Frothingham R, *et al*. Phylogeny of the Whipple's-disease-associated bacterium. *Lancet* 1991;**328**:474–5.
7 Relman DA, Schmidt TM, MacDermott RP, *et al*. Identification of the uncultured bacillus of Whipple's disease. *N Engl J Med* 1992;**327**:293–301.
8 Maizel H, Ruffin JM, Dobbins WO. Whipple's disease: a review of 19 patients from one hospital and a review of the literature since 1950. *Medicine* 1970;**49**:175–205.
9 Lynch T, Odel J, Fredericks DN, *et al*. Polymerase chain reaction-based detection of Tropheryma whippelii in central nervous system Whipple's disease. *Ann Neurol* 1997;**42**: 120–4.
10 Ramzan NN, Loftus E, Burgart LJ, *et al*. Diagnosis and monitoring of Whipple's disease by polymerase chain reaction. *Ann Intern Med* 1997;**126**:520–7.
11 Dobbins WO. Whipple's disease: an historical perspective. *Q J Med* 1985;**56**:523–31.
12 Gaist D, Ladefoged K. Whipple's disease [review]. *Scand J Gastroenterol* 1994;**29**:97–101.
13 Durand DV, Lecomte C, Cathebras P, *et al*. Whipple disease. Clinical review of 52 cases. The SNFMI Research Group on Whipple Disease. *Medicine* 1997;**76**:170–84.
14 Gross JB, Wollaeger EE, Sauer WG, *et al*. Whipple's disease. Report of four cases including two in brothers, with observations on pathologic physiology, diagnosis and treatment. *Gastroenterology* 1959;**36**:65–93.
15 Dobbins WO. *Whipple's disease*. Springfield IL: Charles C Thomas, 1987.
16 Isenberg JI, Gilbert SB, Pitcher JL. Ascites with peritoneal involvement in Whipple's disease. Report of a case. *Gastroenterology* 1971;**60**:305–10.
17 Chears WC, Smith AG, Ruffin JM. Diagnosis of Whipple's disease by peripheral lymph node biopsy: report of a case. *Am J Med* 1959;**27**:351–3.
18 Kraunz RF. Whipple's disease with cardiac and renal abnormalities. *Arch Intern Med* 1969;**123**:701–6.
19 Clancy RL, Tomkins WA, Muckle TJ, *et al*. Isolation and characterisation of an aetiological agent in Whipple's disease. *BMJ* 1975;iii:568–70.
20 McAllister HA, Fenoglio JJ. Cardiac involvements in Whipple's disease. *Circulation* 1975;**52**:152–6.
21 Johnson L, Diamond I. Cerebral Whipple's disease. Diagnosis by brain biopsy. *Am J Clin Pathol* 1980;**74**:486–90.
22 Knox DL, Green WR, Troncoso JC, *et al*. Cerebral ocular Whipple's disease: a 62-year odyssey from death to diagnosis. *Neurology* 1995;**45**:617–25.
23 Hawkins CF, Farr M, Morris CJ, *et al*. Detection by electron microscope of rod-shaped organisms in synovial membrane from a patient with the arthritis of Whipple's disease. *Ann Rheum Dis* 1976;**35**:502–9.
24 Pirola RC, Mishkel MA, Macdonald GJ, *et al*. Whipple's disease. *Med J Aust* 1967;**2**:985–8.
25 Samuels T, Hamilton P, Shaw P. Whipple disease of the mediastinum. *Am J Roentgenol* 1990;**154**:1187–8.
26 Mendel E, Khoo LT, Go JL, *et al*. Intracerebral Whipple's disease diagnosed by stereotactic biopsy: a case report and review of the literature. *Neurosurgery* 1999;**44**:203–9.
27 Nishimura JK, Cook BE, Pach JM. Whipple disease presenting as posterior uveitis without prominent gastrointestinal symptoms. *Am J Ophthalmol* 1998;**126**: 130–2.
28 Moorthy S, Nolley G, Hermos JA. Whipple's disease with minimal intestinal involvement. *Gut* 1977;**18**:152–5.
29 Mansbach CM, Shelburne JD, Stevens RD, *et al*. Lymph-node bacilli form bodies resembling those of Whipple's disease in a patient without intestinal involvement. *Ann Intern Med* 1978;**89**:64–6.

30 Wilcox GM, Tronic BS, Schecter DJ, *et al*. Periodic acid-Schiff-negative granulomatous lymphadenopathy in patients with Whipple's disease. Localization of the Whipple bacillus to noncaseating granulomas by electron microscopy. *Am J Med* 1987;**83**:165–70.
31 James TN, Bulkley BH, Kent SP. Vascular lesions of the gastrointestinal system in Whipple's disease. *Am J Med Sci* 1984;**288**:125–9.
32 Feldman M, Price G. Intestinal bleeding in patients with Whipple's disease. *Gastroenterology* 1989;**96**:1207–9.
33 Fleming JL, Wiesner RH, Shorter RG. Whipple's disease: clinical, biochemical and histopathological features and assessment of treatment in 29 patients. *Mayo Clin Proc* 1988;**63**:539–51.
34 LeVine ME, Dobbins WO. Joint changes in Whipple's disease. *Semin Arthritis Rheum* 1973;**3**:79–93.
35 Canoso JJ, Saini M, Hermos JA. Whipple's disease and ankylosing spondylitis: simultaneous occurrence in HLA-B27 positive male. *J Rheumatol* 1978;**5**:79–84.
36 Swash M, Schwartz MS, Vandenburg MJ, *et al*. Myopathy in Whipple's disease. *Gut* 1977;**18**:800–4.
37 Cruz-Martinez A, Gonzalez P, Garza E, *et al*. Electrophysiologic follow-up in Whipple's disease. *Muscle Nerve* 1987;**10**:616–20.
38 Smith WT, French JM, Gottsman M, *et al*. Cerebral complications of Whipple's disease. *Brain* 1965;**88**:137–49.
39 Vlietstra RE, Lie JT, Kuhl WE, *et al*. Whipple's disease involving the pericardium: pathological confirmation during life. *Aust NZ J Med* 1978;**8**:649–51.
40 Louis ED, Lynch T, Kaufman P, *et al*. Diagnostic guidelines in central nervous system Whipple's disease. *Ann Neurol* 1996;**40**:561–8.
41 Verhagen WIM, Huygen PLM, Dalman JE, *et al*. Whipple's disease and the central nervous system. A case report and review of the literature. *Clin Neurol Neurosurg* 1996;**98**:299–304.
42 Sieracki JC, Fine G, Horn RC, *et al*. Central nervous system involvement in Whipple's disease. *J Neuropathol Clin Neurol* 1960;**19**:70–5.
43 Riggs JE. The evolving natural history of neurologic involvement in Whipple disease: a hypothesis [letter]. *Arch Neurol* 1988;**45**:830.
44 Knox DL, Bayless TM, Pittman FE. Neurologic disease in patients with treated Whipple's disease. *Medicine* 1976;**55**:467–76.
45 Romanul FCA, Radvany J, Rosales RK. Whipple's disease confined to the brain: a case studied clinically and pathologically. *J Neurol Neurosurg Psychiatry* 1977;**40**:901–9.
46 Schwartz MA, Selhorst JB, Ochs AL, *et al*. Oculomasticatory myorhythmia: a unique movement disorder occurring in Whipple's disease. *Ann Neurol* 1986;**20**:677–83.
47 Dobbins WO. Whipple's disease [editorial]. *Mayo Clin Proc* 1988;**63**:623–4.
48 Brown AP, Lane JC, Murayama S, *et al*. Whipple's disease presenting with isolated neurological symptoms. *J Neurosurg* 1990;**73**:623–7.
49 Schmitt BP, Richardson H, Smith E, *et al*. Encephalopathy complicating Whipple's disease: failure to respond to antibiotics. *Ann Intern Med* 1981;94:51–2.
50 Silbert SW, Parker E, Horenstein S. Whipple's disease of the central nervous system. *Acta Neuropathol* 1976;**36**:31–8.
51 Grotta JC, Pettigrew LC, Schmidt WA, *et al*. Oculomasticatory myorhythmia [letter]. *Ann Neurol* 1987;**22**:395–6.
52 Hausser-Hauw C, Roullet E, Robert R, *et al*. Oculo-facio-skeletal myorhythmia as a cerebral complication of systemic Whipple's disease. *Mov Disord* 1988;**3**:179–84.
53 Adler CH, Galetta SL. Oculo-facial-skeletal myorhythmia in Whipple disease: treatment with ceftriaxone. *Ann Intern Med* 1990;**112**:467–9.
54 Simpson DA, Wishnow R, Gargulinski RB, *et al*. Oculofacial-skeletal myorhythmia in central nervous system Whipple's disease: additional case and review of the literature. *Mov Disord* 1995;**10**:195–200.
55 Avila MP, Jalkh AE, Feldman E, *et al*. Manifestations of Whipple's disease in the posterior segment of the eye. *Arch Ophthalmol* 1984;**102**:384–90.
56 Leland TM, Chambers JK. Ocular findings in Whipple's disease. *South Med J* 1978;**71**:335–8.
57 Feldman M, Hendler RS, Morrison EB. Acute meningoencephalitis after withdrawal of antibiotics in Whipple's disease. *Ann Intern Med* 1980;**93**:709–11.
58 Bjerknes R, Odegaard S, Bjerkvig R, *et al*. Whipple's disease. Demonstration of a persisting monocyte and macrophage dysfunction. *Scand J Gastroenterol* 1988;**23**:611–19.
59 Ectors NL, Geboes KJ, de Vos RM, *et al*. Whipple's disease: a histological, immunocytochemical, and electron microscopic study of the small intestinal epithelium. *J Pathol* 1994;**172**:73–9.
60 Marth T, Roux M, von Herbay A, *et al*. Persistent reduction of complement receptor 3 α-chain expressing mononuclear blood cells and transient inhibitory serum factor in Whipple's disease. *Clin Immunol Immunopathol* 1994;**72**:217–26.
61 Bai JC, Sen L, Diez R, *et al*. Impaired monocyte function in patients successfully treated for Whipple's disease. *Acta Gastroenterol Latinoam* 1996;**26**:85–9.
62 Marth T, Nuerath M, Cuccerini B, *et al*. Defects of monocyte interleukin-12 production and humoral immunity in Whipple's disease. *Gastroenterology* 1997;**113**:442–8.
63 Marth T, Strober W. Whipple's disease. *Semin Gastroenterol Dis* 1996;**7**:41–8.
64 Eck M, Kreipe H, Harmsen D, *et al*. Invasion and destruction of mucosal plasma cells by Tropheryma whippelii. *Hum Pathol* 1997;28:1424–8.
65 Mayberry J, Furness P, Austin M, *et al*. Endoscopic appearances in Whipple's disease. *J R Soc Med* 1986;79:483–5.
66 Geboes K, Ectors N, Heidbuchel H, *et al*. Whipple's disease: the value of upper gastrointestinal endoscopy for the diagnosis and follow-up. *Acta Gastroenterol Belg* 1992;**55**:209–19.
67 Rice RP, Roufail WM, Reeves RJ. The roentgen diagnosis of Whipple's disease (intestinal lipodystrophy), with emphasis on improvement following antibiotic therapy. *Radiology* 1967;**88**:295–301.
68 von-Herbay A, Ditton HJ, Maiwald M. Diagnostic application of a polymerase chain reaction assay for the Whipple's disease bacterium to intestinal biopsies. *Gastroenterology* 1996;**110**:1735–43.
69 Pron B, Poyart C, Abachin E, *et al*. Diagnosis and follow-up of Whipple's disease by amplification of the 16S rRNA gene of Tropheryma whippelii. *Eur J Clin Microbiol Infect Dis* 1999;**18**:62–5.
70 Ehrbar H-U, Bauerfeind P, Dutly F, *et al*. PCR-positive tests for Tropheryma whippelii in patients without Whipple's disease [letter]. *Lancet* 1999;**353**:2214.
71 Hinrikson HP, Dutly F, Altwegg M. Homogeneity of 16S-23S ribosomal intergenic spacer regions of Tropheryma whippelii in Swiss patients with Whipple's disease. *J Clin Microbiol* 1999;**37**:152–6.
72 Misbah SA, Stirzaker D, Ozols B, *et al*. Anonymous survey of blood donors by polymerase chain reaction for Tropheryma whippelii. *Q J Med* 1999;**92**:61.
73 Gross M, Jung C, Zoller WG. Detection of Tropheryma whippelii DNA (Whipple's disase) in faeces. *Ital J Gastroenterol Hepatol* 1999;**31**:70–2.
74 Keinath RD, Merrell DE, Vlietstra R, *et al*. Antibiotic treatment and relapse in Whipple's disease. Long-term follow-up of 88 patients. *Gastroenterology* 1985;**88**:1867–73.
75 Schnider PJ, Reisinger EC, Berger T, *et al*. Treatment guidelines in central nervous system Whipple's disease [letter]. *Ann Neurol* 1997;**41**:560–1.
76 Singer R. Diagnosis and treatment of Whipple's disease [review]. *Drugs* 1998;**55**:699–704.
77 Denholm RB, Mills PR, More IA. Electron microscopy in the long-term follow-up of Whipple's disease. Effect of antibiotics. *Am J Surg Pathol* 1981;**5**:507–16.
78 Davis TD, McBee JW, Borland JL, *et al*. The effect of antibiotics and steroid therapy on Whipple's disease. *Gastroenterology* 1963;**44**:112–16.
79 Rijke AM, Falke TH, de-Vries RR. Computed tomography in Whipple disease. *J Comput Assist Tomogr* 1983;7:1101–2.
80 Schneider T, Stallmach A, von Herbay A, *et al*. Treatment of refractory Whipple disease with interferon-γ. *Ann Intern Med* 1998;**129**:875–7.
81 Morningstar WA. Whipple's disease. An example of the value of the electron microscope in diagnosis, follow-up and correlation of a pathologic process. *Hum Pathol* 1975;**6**:443–54.
82 von-Herbay A, Ditton HJ, Schuhmacher F, *et al*. Whipple's disease: staging and monitoring by cytology and polymerase chain reaction analysis of cerebrospinal fluid. *Gastroenterology* 1997;**113**:434–41.