Whipple's Disease

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Patient Vignettes

Patient 1

A 55-year-old man developed right facial twitching without other neurological signs. Hemifacial spasm was diagnosed. Carbamazepine (600 mg daily) and baclofen (60 mg daily) produced no benefit. Five months later, he complained of somnolence, blurred vision, and poor balance. One month later, the facial twitching spread to his neck and tongue, persisting with sleep. He developed dysarthria and complained of poor memory, change in personality, malaise, intermittent fevers, increased sweating, impotence, and inability to ejaculate. One year after the onset of facial twitching, orientation, memory, and language were normal. He was intermittently inattentive and had marked dysarthria due to rhythmic lingual retraction and masticatory myorhythmia coinciding with rhythmic contraction of the right side of the face, neck, and chest and right arm. The contractions spread irregularly to the left side of the face, chest, and left arm and leg. Vertical gaze was limited but

Supplementary Information The online version of this chapter (https://doi.org/10.1007/978-3-030-75898-1_28) contains supplementary material, which is available to authorized users.

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S. J. Frucht (ed.), *Movement Disorder Emergencies*, Current Clinical Neurology,
https://doi.org/10.1007/978-3-030-75898-1_28

improved with the oculocephalic maneuver. Saccades were slow in all directions. Pendular vergence oscillations of the right more than of the left eye (frequency = 1 Hz) were synchronous with the masticatory and skeletal myorhythmia (i.e., oculofacial-skeletal myorhythmia [OFSM]). Electromyographic analysis revealed 400-msec bursts of bilateral rhythmic activity. This activity originated at the level of cranial nerve VII, and spread rostrally to involve the muscles of the mastication, and caudally to involve muscles of the neck, arms, and legs. Muscle tone, strength, sensation, deep tendon reflexes, plantar responses, and postural stability were normal. Gait was mildly ataxic.

Serum chemistries; complete blood count (CBC); serum venereal disease research laboratory (VDRL) test result; serum Lyme titer; thyroid function test (TFT) results; antinuclear antibody (ANA) titer; human immunodeficiency virus (HIV) test result; vitamin B12 (B12); folate; CSF cell count, protein, and glucose levels; and electroencephalogram (EEG) were normal. Brain magnetic resonance imaging (MRI) with gadolinium revealed a left frontal periventricular punctate hyperintensity. Technetium-99m hexamethylpropyleneamine oxime (99m Tc = HMPAO) single-photon emission computed tomography (SPECT) revealed decreased activity in the right cerebellar hemisphere. A duodenal biopsy specimen obtained 12 months after the onset of facial twitching was initially normal (periodic acid Schiff [PAS] stain negative, electron microscopy [EM] not performed). After 1 month, a repeat biopsy with Crosby capsule revealed foamy macrophages stained positive with PAS and silver stains and negatively with acid-fast stain. PAS and Grocott methenamine silver stains demonstrated intracytoplasmic granular rod-shaped structures consistent with Whipple's bacillus. Probable CNS WD was diagnosed.

Trimethoprim-sulfamethoxazole (TPM-SMX) (1 double-strength [DS] tablet twice a day) resulted in improvement in malaise and the ocular component of the myorhythmia. When diarrhea developed, TPM-SMX was discontinued, and intravenous ceftriaxone (2 gm daily) resulted in resolution of the diarrhea and sweating, decrement in the myorhythmia, and increase in alertness. After 1 month, he was switched to receive doxycycline monohydrate (200 mg twice a day), with worsening of hemifacial spasms, malaise, and lethargy over the ensuing 9 months. Ceftriaxone (2 gm/day) was resumed, with improvement in hemifacial spasms, malaise, and lethargy over the ensuing 3 months. After 2 years of follow-up, he was taking TPM-SMX (1 DS tablet twice a day). He still had right facial twitching, complaints of poor memory, increased sweating, impotence, and inability to ejaculate. There was moderate improvement in limb myorhythmia, malaise, and vertical gaze.

Patient 2

A 47-year-old woman developed severe progressive insomnia unresponsive to medication, a 10-lb weight loss, double vision, fever, and submandibular lymph node enlargement. Past history was notable for arthritis. No diarrhea, steatorrhea, or other

gastrointestinal symptoms were reported. She noted spontaneous rhythmic right eye movement while looking in the mirror. On examination, vertical and horizontal saccades were slow, with diminished abduction of the left eye. Downgaze was full; upgaze was mildly limited. There were spontaneous convergent nystagmoid movements in the right eye unaccompanied by miosis. These movements increased with downward moving optokinetic stimuli.

Over the ensuing 8 months, a progressive ophthalmoparesis resulted in complete loss of voluntary eye movements except for adduction of the right eye. She developed short-term memory loss, depressive symptoms, difficulty swallowing, blurred vision, intermittent hypersomnolence, and increased postural instability. On reexamination, she was intermittently unrousable, with hypomimia and severe dysarthria. Pendular vergence oscillations of both eyes synchronous with the masticatory myorhythmia (oculomasticatory myorhythmia [OMM]) were present. There was mild hypertonia, and normal strength and sensation. Deep tendon reflexes were brisk. Gait was slow, with shuffling, difficulty turning, and postural instability. Levodopa-carbidopa and prednisolone (20 mg daily) were trialled without benefit.

Serum chemistries, CBC, serum Lyme titers, coagulation screen results, ANA titer, B12 and folate levels, TFT results, serum protein electrophoresis, and VDRL and HIV test results were normal. EEG revealed a generalized mildly slow background. CSF analyses revealed protein levels of 50 to 55 mg/dl with a normal glucose concentration, and 0 to 70 PAS-negative mononuclear cells. Brain computed tomography (CT) scans appeared normal, and MRI revealed an Arnold-Chiari type 1 malformation with no brainstem compression. Specimens obtained at two duodenal biopsies indicated mild chronic nonspecific duodenitis. No PAS staining or other changes consistent with WD were detected. EM was not performed, but polymerase chain reaction (PCR) on gut biopsy samples was positive, even though PAS staining was negative. CNS WD was diagnosed based on clinical findings (i.e., OMM). Intravenous ceftriaxone (2 gm daily) for 6 months resulted in complete resolution of OMM and improvement in the supranuclear gaze palsy and malaise. After switching to TPM-SMX (1 DS tablet twice a day), the supranuclear gaze palsy, lethargy, and malaise recurred. After years of follow-up, she was restricted to a wheelchair and fed by gastrostomy tube.

Introduction

First described by George Hoyt Whipple in 1907 [1], Whipple's disease is a chronic, treatable multisystemic infectious disease caused by the gram-positive actinomycete, *Tropheryma whipplei*. Over a century has elapsed since its first recognition, yet Whipple's disease remains a somewhat enigmatic diagnostic challenge. In the central nervous system in particular, Whipple's disease (WD) can mimic almost any other neurologic condition. Diagnosis of WD remains complicated and laborious. Equally, because of a variety of factors, most notably its penchant for the intracellular milieu and slow replication rate, treatment is far from straightforward, requiring prolonged courses of antibiotics, the choice of which is generally informed by

limited clinical experience rather than controlled trial evidence. In this chapter, we review the diagnostic conundrum that is Whipple's disease of the central nervous system, touch on the immunopathologic defects which promote transition from asymptomatic carriage to a disease state, highlight red flags which should make clinicians suspect the diagnosis, and conclude with insights from previous treatment trials.

Whipple's is a particular challenge: difficult to diagnose, pleomorphic in its presentations, and requiring prolonged treatment.

Tropheryma whipplei

Previously considered a rare organism, more recent studies have shown that *T. whipplei* is in fact a common commensal bacterium. This bacilliform bacterium is found ubiquitously in the environment, with highest prevalence in sewage and wastewaters [2]. Transmission likely occurs through the fecal-oral route, and it is likely that most individuals are exposed to the bacterium at some point in their lifetime. Nearly a century would elapse between the original description by Whipple and the eventual identification of the causative bacillus. Sequencing of PCR-amplified bacterial 16s ribosomal RNA from infected tissue, followed by sequencing of other parts of its genome, confirmed the bacillus as a GC-rich gram-positive actinomycete [3–6]. The determination of specific nucleotide sequences within the *T. whipplei* genome also allowed the development of sensitive and specific PCR tools which are now critical in diagnosing both systemic and CNS forms of the disorder [7–9]. The bacterium is predominantly found intracellularly in macrophages and monocytes of affected tissues, though it can also persist extracellularly [10]. Histologically, it generally appears as multiple periodic acid-Schiff (PAS) positive, diastase-resistant inclusions in macrophage cytoplasm [11]. Examination by electron microscopy demonstrates that the areas of intense PAS staining are packed with bacilli, some degenerated.

Epidemiology

Classic Whipple's disease is predominantly a disorder of middle-aged Caucasian men (outnumbering women 8:1), though this is less obvious in the cases reported with predominant CNS manifestations [12]. Farmers and those in regular contact with soil or animals also have a much higher incidence of Whipple's disease [11]; close contact with affected individuals and squalid sanitary conditions also increase the risk [12–14]. Seroprevalence for *T. whipplei* is over 70% in the general population, though most individuals clear the infection. Asymptomatic gastrointestinal carriage is also not uncommon, ranging from 1.5% to 7% in the general population to 12% to 25% in sewage treatment workers [2, 13, 15, 16]. Despite high

seroprevalence and asymptomatic carriage rates, Whipple's disease itself remains exceedingly rare, with estimated incidence of less than 1 per 1,000,000 population per year [11]. Such great discrepancy between high levels of exposure/asymptomatic carriage and the tiny number of people that develop disease suggests a strong role for host factors in pathogenesis of disease. In this regard, genetic factors, particularly relating to host cell-mediated immune responses, appear to play a critical role in conferring a lifetime susceptibility to Whipple's disease [17].

Pathophysiology and Immunopathology

The immunopathogenesis of Whipple's disease remains incompletely understood. At its core, it is accepted that dysfunctional macrophage and monocyte function resulting in impaired clearance of the bacterium are at play [18–20]. Such impairments are probably majorly genetically determined, with rare familial cases, disease predominance in Caucasians, specific HLA associations (HLA DRB1*13 and DQB1*06) known to impair antigen presentation, and polymorphisms in certain cytokine genes polarizing immune responses toward T-helper 2 (TH2) activity being associated with the disease [21, 22]. Furthermore, some patients are prone to recurrent relapses with different strains of *T. whipplei* [23]. Moreover, acquired immune deficits have also been recognized as a risk factor for WD. Patients with HIV may be at increased risk [24, 25], as may those receiving the increasingly common biologic therapies for systemic inflammatory disorders [26, 27].

Under normal circumstances, exposure to *T. whipplei* results in a swift and robust immune response resulting in clearance of the organism, or at the very least, asymptomatic carriage. In patients developing WD, however, this response is muted, either due to inherently defective monocyte function or through dysfunctional priming of *T. whipplei*-specific T cells by dendritic cells in the gut, perhaps from inadequate IL-12 production [20, 28]. This failure to clear the organism sets the scene for persistent bacterial replication within gut monocytes and spread to cause systemic disease. In the case of central nervous system disease, entry might be achieved through passage of infected monocytes across the blood-brain barrier [29].

Numerous defective immune responses have been noted in patients with WD. These include impairments of fusion of *T. whipplei* containing phagosomes with lysosomes [30], low serum concentrations of interleukin-12 (which likely inhibits the generation of TH1-helper cells), and overexpression of IL-10 [31–33]. Additionally, there appears to be a significant role for IL-16 in the immunopathogenesis of WD. *T. whipplei* itself stimulates the release of IL-16 from macrophages, which induces macrophage apoptosis and impairs phagosome-lysosome fusion [34, 35]; interestingly, IL-16 levels and apoptotic markers correlate with disease severity and decrease to normal upon successful treatment [30, 36]. *T. whipplei* has been shown to replicate in macrophages and monocytes deactivated with IL-16, while anti-IL-16 antibodies inhibit *T. whipplei* replication [34].

Clinical Presentations of Whipple's Disease

The clinical manifestations of Whipple's disease are insidious in onset, slowly progressive, and, for the most part, highly nonspecific. This often leads to significant delays in diagnosis. Classic Whipple's disease generally begins with a period of intermittent, migratory large joint seronegative arthralgia or arthritis, which generally spans a number of years prior to the development of other symptoms [27]. Predilection for large joints is often seen, with knees, wrists, and ankles affected more often than shoulders or hips [37]. Generally, the ensuing symptoms are gastrointestinal in nature, consisting of weight loss, diarrhea, and steatorrhea. This may be accompanied by intermittent fever and lymphadenopathy. Cardiac involvement is common and may comprise valvular dysfunction, coronary arterial damage, culture-negative endocarditis as well as myocarditis and pericarditis [38–40]. Rarer disease manifestations include increased skin pigmentation, subcutaneous nodules, and bone marrow involvement [41, 42]. Various ocular manifestations of Whipple's disease have been described including uveitis, vitritis, retinitis, keratitis, and optic neuritis [11, 43], which may cause diagnostic confusion with other eye-involving multisystem masqueraders including syphilis and vasculitides.

Neurological Manifestations of Whipple's Disease

Neurological involvement occurs in 10% to 40% of patients with Whipple's disease [44]. In the vast majority of cases, this occurs as a late feature of systemic Whipple's disease, less commonly as a CNS relapse in patients with previously treated systemic Whipple's disease treated, and in exceptional cases as isolated CNS Whipple's disease [44]. Spinal cord and peripheral nerve involvement are also reported [45, 46]. Asymptomatic CNS infection may occur, and even in the absence of neurological symptoms, up to 50% of patients with Whipple's disease are found to have CNS infection by PCR analysis of the CSF [47]. Presenting clinical symptoms are protean. A progressive encephalopathy manifesting as dementia, confusion, apathy, and somnolence is probably the most common neurological sign [44]. Supranuclear ophthalmoplegia, psychiatric symptoms, myoclonus, and gait ataxia are also suggestive [43, 48]. Seizures can occur, as can focal neurological signs resulting from focal mass lesions or strokes secondary to Whipple endocarditis. Hypothalamic dysfunction with secondary hormonal imbalance is common.

Two clinical signs, namely, oculomasticatory myorhythmia (OMM) and oculofacial-skeletal myorhythmia (OFSM), are highly specific for Whipple's disease, especially in the presence of supranuclear gaze palsy [49–51]. Present in about 20% of patients with CNS WD, OMM involves pendular vergence oscillations of the eyes synchronous with rhythmic myoclonic contractions of the masticatory muscles, while OFSM additionally involves contraction of the skeletal musculature;

both are classically thought of as pathognomonic of CNS Whipple's disease [43, 50, 52]. Pendular vergence oscillations are characterized by continuous smooth, rhythmic convergent eye movements with a frequency of 1 Hz varying from 10 to 25 degrees of amplitude per eye, but never diverging beyond the primary position. The oscillations continue throughout sleep and may be subtle and asymmetric. Convergence and divergence are at the same speed and are not accompanied by miosis or accommodation. The anatomical basis for this apparently unique movement disorder is not known but may originate from the upper brainstem. Though myorhythmia as an entity can occur in a number of other conditions, including brainstem and thalamic strokes or structural lesions, its oculomasticatory and oculofacial-skeletal variants do appear to be pathognomonic for WD [53].

Pendular vergence nystagmus, oculomasticatory myorhythmia, and oculofacial-skeletal myorhythmia are unusual but pathognomonic findings in Whipple's disease.

Radiologic Findings

Neuroimaging findings in CNS Whipple's disease are equally as diverse as the clinical manifestations. Importantly, even in the presence of florid clinical signs, brain imaging can be normal [54, 55]. For unknown reasons, there is a predilection for involvement of the diencephalon, and CNS Whipple's is an important differential diagnosis of abnormalities in the brainstem, hypothalamus, and thalamus [54]. Indeed, T2-signal hyperintensity involving these regions either symmetrically or asymmetrically, occasionally extending into the adjacent medial temporal lobes, is the most commonly observed abnormality [54]. Mild-to-moderate cerebral atrophy is thought to be present in about half of cases [54]. Focal or multifocal mass lesions, which tend to show little if any enhancement, may also be seen and may mimic CNS neoplasms [56–58]. Less frequently, leptomeningeal enhancement, stroke-like lesions, or spinal cord involvement may be observed [45, 59]. Signal hyperintensity in the corticospinal tracts on T2-weighted imaging is not uncommon.

Investigations and Diagnosis

Most cases of Whipple's disease are diagnosed based on gut biopsy findings. As most patients with suspected CNS Whipple's disease will have concurrent systemic involvement, this approach to diagnosis generally proceeds in parallel with confirmation of CNS involvement and sampling other clinically involved sites. The cerebrospinal fluid is the medium of choice on which to confirm CNS Whipple's disease, though brain biopsy is occasionally required if systemic involvement is absent,

clinical suspicion is high, and CSF studies are unrevealing. Given that CNS involvement is described in around 50% of cases, sometimes without clinical correlate, CSF sampling is recommended in all cases as this will influence treatment decisions [39, 40]. The general laboratory workup of patients with CNS Whipple's disease frequently reveals steatorrhea, impaired xylose absorption, anemia, and hypoalbuminemia, reflecting gut dysfunction (though this will be absent in isolated CNS disease). The hallmark of disease is the finding of *T. whipplei*-infected macrophages which stain positive with PAS and are diastase resistant. Immunohistochemical stains using specific antibodies against *T. whipplei* increase diagnostic sensitivity and may be positive in the absence of PAS-positive staining [60]. Though PCR amplification of *T. whipplei* DNA from stool and saliva is often positive in cases of Whipple's disease, given that asymptomatic gut carriage of *T. whipplei* can occur, a positive gut PCR alone is not diagnostic, and diagnosis always requires a second method of confirmation. The same is not true for sterile sites such as the CSF. Serum *T. whipplei* antibody titers are paradoxically low in patients with WD, rendering this a useless test in this setting.

Cerebrospinal fluid cell count and protein are, more often than not, normal. A moderate pleocytosis and CSF protein elevation may however be observed [43, 55]. PAS staining of the CSF has an equally low yield (positive in about a third of cases). *T. whipplei* PCR on the other hand is highly sensitive (>90%) [55]. Electron microscopy can be used to visualize *T. whipplei* in infected tissues, though it is only available in specialist laboratories and does not form part of routine clinical workup in this condition [39].

Treatment

Prior to its first successful treatment with antibiotics in 1952 [61], Whipple's disease was a universally fatal affliction. For decades thereafter, choices of antibiotic regimes remained poorly informed, and indeed it was only after sequencing of the organism's genome and successful culture of *T. whipplei* in the early 2000s (allowing in vitro testing of antibiotic sensitivity) that its antibiotic susceptibility was defined. Tetracycline was the treatment of choice for many years, until the recognition of alarmingly high relapse rates (especially CNS relapses) with this therapy alone [62]. For this reason, induction therapy with 2 weeks of parenteral high-dose penicillin, third-generation cephalosporins, or carbapenems (antibiotics which achieve high CNS concentrations) is often advocated [11]. Maintenance therapy

should generally continue for at least 1 year. Trimethoprim-sulfamethoxazole was previously considered the optimal maintenance strategy following induction; however, evidence now suggests that this may not be the case. Indeed trimethoprim has no action against *T. whipplei*, as the bacterium lacks the gene coding for dihydrofolate reductase, the target of trimethoprim [63]. Recent in vitro studies have also suggested that up to a quarter of *T. whipplei* strains may be resistant to sulfonamides in vitro [64]. Moreover, acquired sulfamethoxazole resistance due to *folP* mutations (the gene encoding dihydropteroate synthase, the target of sulfonamides) has been described [65].

Recent evidence suggests that a combination of oral doxycycline and hydroxychloroquine for 12 months might be a more effective treatment option [23]. This combination is the only one proven to be bactericidal in vitro and has been successfully used in two patients with CNS relapses in whom co-trimoxazole was ineffective [65, 66]. After 12 months of dual therapy, long-term (possibly lifelong) oral doxycycline is advocated by some authors, in order to prevent late relapses or reinfection in susceptible patients [55, 67].

Whipple's disease, whether systemic or localized, should be regarded as a chronic disease prone to relapse. As such, patients should undergo lifelong follow-up in order to identify both relapses and complications of treatment early and institute appropriate management without delay [39, 68, 69]. Most cases of CNS relapse occur late (beyond 2 years), and it is important to recognize that relapses can occur at sites distant from the originally affected organ. After completion of treatment for CNS WD, performing *T. whipplei* PCR on CSF is currently the preferred method for confirming treatment efficacy and eradication of the bacterium from the central nervous system. The most common complication arising from treatment of Whipple's disease is the development of a nonspecific inflammatory syndrome termed IRIS (immune reconstitution inflammatory syndrome) [70]. This complication occurs almost exclusively in patients receiving immunosuppressive therapy (generally following misdiagnosis of their condition as a cryptogenic inflammatory arthritis) prior to starting antibiotics [70, 71]. IRIS may manifest as prolonged fever along with other signs and symptoms of systemic inflammation, e.g., arthritis, orbitopathy, and gut perforation, after initiation of treatment. It occurs in approximately 10% of patients but can have a rapid and fatal course. It generally responds promptly to the addition of oral corticosteroids, which may be life-saving [39].

See Table 28.1 for modified guidelines for diagnostic screening, biopsy, and treatment of CNS Whipple's disease.

Table 28.1 Modified guidelines for diagnostic screening, biopsy, and treatment of CNS Whipple's disease [43]

Definite CNS Whipple's disease
Must have any one of the following three criteria:
1. Oculomasticatory myorhythmia or oculofacial-skeletal myorhythmia and/or pendular vergence nystagmus
2. Positive brain tissue biopsy
3. Positive PCR analysis of cerebrospinal fluid
4. Autopsy-confirmed diagnosis
Probable CNS Whipple's disease
1. Suggestive neurological symptoms and signs (cognitive decline, personality change, supranuclear gaze palsy, etc.)
And
Positive PCR analysis of duodenal tissue
Or
PAS-positive macrophages in duodenal biopsy
+/− Supportive imaging
Possible CNS Whipple's disease
Must have any one of four systemic symptoms, not due to another known etiology:
1. Fever of unknown etiology
2. Gastrointestinal symptoms (steatorrhea, abdominal distension, or pain)
3. Chronic migratory arthralgias or polyarthralgias
4. Unexplained lymphadenopathy, night sweats, or malaise
And
Must have any one of four neurological signs, not due to another known etiology:
1. Supranuclear vertical gaze palsy
2. Rhythmic myoclonus
3. Dementia with psychiatric symptoms
4. Hypothalamic manifestations
Suggested diagnostic sequence
Clinical presentation suggestive (but not pathognomonic) of Whipple's disease (cognitive dysfunction, personality change, weight loss, diarrhea, arthralgia)
Proceed to:
1. Detailed neurological examination: including evaluation for rhythmic myoclonus, supranuclear gaze palsy, pendular vergence nystagmus, cerebellar ataxia
2. Laboratory investigations: hypoalbuminemia, steatorrhea, anemia
3. Neuroimaging: MRI brain with gadolinium including diffusion-weighted imaging
Suggestive clinical +/− biochemical and radiological features
->Proceed to confirm diagnosis:
1. Small bowel biopsy: PAS staining of small intestinal mucosal cells and PCR of gut biopsy sample
2. Cerebrospinal fluid examination including PCR for *T. whipplei*
3. If discreet lesion on imaging, proceed to stereotactic biopsy to outrule neoplasm, and confirm diagnosis (if CSF PCR is negative or if patient fails to respond to appropriate antibiotic therapy)
4. Sampling of any other clinically involved sites
Diagnosis confirmed
1st line
1. Hydroxychloroquine 200 mg TDS *and* doxycycline 200 mg/day for 12 months
Followed by
2. Doxycycline 200 mg/day lifelong
2nd line
1. Intravenous meropenem 1g TDS for 14 days or ceftriaxone 2g OD for 14 days
Followed by
2. Trimethoprim-sulfamethoxazole 960 mg twice daily by mouth for 12 months

Conclusion

Whipple's disease is a rare infectious disorder that may first be recognized by a neurologist or movement disorder clinician. As a treatable condition, like Wilson's disease, it is important to maintain a high index of suspicion.

Acknowledgments Dr. John Lynch died at a young age in 2019. He contributed hugely to the care of patients in the West of Ireland and to the education of a generation of medical and nursing students in Ireland. We all miss John's enthusiasm, expertise, and infectious laugh. It was always an absolute pleasure to work on this chapter with John over the years. As a colleague said, "we lost one of the good ones."

References

1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. Bull Johns Hopkins Hosp 1907.
2. Schöniger-Hekele M, Petermann D, Weber B, Müller C. Tropheryma whipplei in the environment: survey of sewage plant influxes and sewage plant workers. Appl Environ Microbiol. 2007;73(6):2033–5. https://doi.org/10.1128/AEM.02335-06.
3. Bentley SD, Maiwald M, Murphy LD, Pallen MJ, Yeats CA, Dover LG, et al. Sequencing and analysis of the genome of the Whipple's disease bacterium Tropheryma whipplei. Lancet. 2003;361(9358):637–44. https://doi.org/10.1016/S0140-6736(03)12597-4.
4. Raoult D, Ogata H, Audic S, Robert C, Suhre K, Drancourt M, et al. Tropheryma whipplei Twist: a human pathogenic actinobacteria with a reduced genome. Genome Res. 2003;13(8):1800–9. https://doi.org/10.1101/gr.1474603.
5. Relman DA, Schmidt TM, Macdermott RP, Falkow S. Identification of the uncultured Bacillus of Whipple's disease. N Engl J Med. 1992;327(5):293–301. https://doi.org/10.1056/NEJM199207303270501.
6. Wilson KH, Frothingham R, Wilson JAP, Blitchington R. Phylogeny of the Whipple's-disease-associated bacterium. Lancet. 1991;338(8765):474–5. https://doi.org/10.1016/0140-6736(91)90545-Z.
7. Lynch T, Odel J, Fredericks DN, Louis ED, Forman S, Rotterdam H, et al. Polymerase chain reaction-based detection of Tropheryma whippelii in central nervous system whipple's disease. Ann Neurol. 1997;42(1):120–4. https://doi.org/10.1002/ana.410420120.
8. 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(6):1735–43. https://doi.org/10.1053/gast.1996.v110.pm8964398.
9. von Herbay A, Ditton H, Schuhmacher F, Maiwald M. Whipple's disease: staging and monitoring by cytology and polymerase chain reaction analysis of cerebrospinal fluid. Gastroenterology. 1997;113(2):434–41. https://doi.org/10.1053/gast.1997.v113.pm9247461.
10. Fredricks DN, Relman DA. Localization of Tropheryma whippelii rRNA in tissues from patients with Whipple's disease. J Infect Dis. 2001;183(8):1229–37. https://doi.org/10.1086/319684.
11. Schneider T, Moos V, Loddenkemper C, Marth T, Fenollar F, Raoult D. Whipple's disease: new aspects of pathogenesis and treatment. Lancet Infect Dis. 2008;8(3):179–90. https://doi.org/10.1016/S1473-3099(08)70042-2.
12. Dobbins W. Whipple's disease. Springfield: Charles C Thomas; 1987.
13. Fenollar F, Puéchal X, Raoult D. Whipple's disease. N Engl J Med. 2007;356(1):55–66. https://doi.org/10.1056/NEJMra062477.

14. Keita AK, Brouqui P, Badiaga S, Benkouiten S, Ratmanov P, Raoult D, et al. Tropheryma whipplei prevalence strongly suggests human transmission in homeless shelters. Int J Infect Dis. 2013;17(1):e67–8. https://doi.org/10.1016/j.ijid.2012.05.1033.
15. Fenollar F, Laouira S, Lepidi H, Rolain J, Raoult D. Value of Tropheryma whipplei quantitative polymerase chain reaction assay for the diagnosis of Whipple disease: usefulness of saliva and stool specimens for first-line screening. Clin Infect Dis. 2008;47(5):659–67. https://doi.org/10.1086/590559.
16. Fenollar F, Trani M, Davoust B, Salle B, Birg M, Rolain J, et al. Prevalence of asymptomatic Tropheryma whipplei carriage among humans and nonhuman primates. J Infect Dis. 2008;197(6):880–7. https://doi.org/10.1086/528693.
17. Lagier JC, Fenollar F, Lepidi H, Raoult D. Evidence of lifetime susceptibility to Tropheryma whipplei in patients with Whipple's disease. J Antimicrob Chemother. 2011;66(5):1188–9. https://doi.org/10.1093/jac/dkr032.
18. Bai JC, Sen L, Diez R, Niveloni S, Mauriño EC, Estevez ME, et al. Impaired monocyte function in patients successfully treated for Whipple's disease. Acta Gastroenterol Latinoam. 1996;26(2):85–9.
19. Desnues B, Ihrig M, Raoult D, Mege JL. Whipple's disease: a macrophage disease. Clin Vaccine Immunol. 2006;13(2):170–8. https://doi.org/10.1128/CVI.13.2.170-178.2006.
20. Marth T, Kleen N, Stallmach A, Ring S, Aziz S, Schmidt C, et al. Dysregulated peripheral and mucosal Th1/Th2 response in Whipple's disease. Gastroenterology. 2002;123(5):1468–77. https://doi.org/10.1053/gast.2002.36583.
21. Biagi F, Badulli C, Feurle GE, Müller C, Moos V, Schneider T, et al. Cytokine genetic profile in Whipple's disease. Eur J Clini Microbiol Infect Dis. 2012;31(11):3145–50. https://doi.org/10.1007/s10096-012-1677-8.
22. Martinetti M, Biagi F, Badulli C, Feurle GE, Müller C, Moos V, et al. The HLA Alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. Gastroenterology. 2009;136(7):2289–94. https://doi.org/10.1053/j.gastro.2009.01.051.
23. Lagier J-C, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment of classic Whipple's disease: from in vitro results to clinical outcome. J Antimicrob Chemother. 2014;69(1):219–27. https://doi.org/10.1093/jac/dkt310.
24. Lozupone C, Cota-Gomez A, Palmer BE, Linderman DJ, Charlson ES, Sodergren E, et al. Widespread colonization of the lung by Tropheryma whipplei in HIV infection. Am J Respir Crit Care Med. 2013;187(10):1110–7. https://doi.org/10.1164/rccm.201211-2145OC.
25. Stein A, Doutchi M, Fenollar F, Raoult D. Tropheryma whipplei pneumonia in a patient with HIV-2 infection. Am J Respir Crit Care Med. 2013;188(8):1036–7. https://doi.org/10.1164/rccm.201304-0692LE.
26. Gaddy JR, Khan ZZ, Chaser B, Scofield RH. Whipple's disease diagnosis following the use of TNF-α blockade. Rheumatology (Oxford). 2012;51(5):946. https://doi.org/10.1093/rheumatology/ker387.
27. Mahnel R, Kalt A, Ring S, Stallmach A, Strober W, Marth T. Immunosuppressive therapy in Whipple's disease patients is associated with the appearance of gastrointestinal manifestations. Am J Gastroenterol. 2005;100(5):1167–73. https://doi.org/10.1111/j.1572-0241.2005.40128.x.
28. Moos V, Schmidt C, Geelhaar A, Kunkel D, Allers K, Schinnerling K, et al. Impaired immune functions of monocytes and macrophages in Whipple's disease. Gastroenterology. 2010;138(1):210–20. https://doi.org/10.1053/j.gastro.2009.07.066.
29. Raoult D, Lepidi H, Harle JR. Tropheryma whipplei circulating in blood monocytes. N Engl J Med. 2001;345(7):548. https://doi.org/10.1056/NEJM200108163450716.
30. Ghigo E, Capo C, Aurouze M, Tung CH, Gorvel JP, Raoult D, et al. Survival of Tropheryma whipplei, the agent of whipple's disease, requires phagosome acidification. Infect Immun. 2002;70(3):1501–6. https://doi.org/10.1128/IAI.70.3.1501-1506.2002.

31. Desnues B, Lepidi H, Raoult D, Mege J. Whipple disease: intestinal infiltrating cells exhibit a transcriptional pattern of M2/alternatively activated macrophages. J Infect Dis. 2005;192(9):1642–6. https://doi.org/10.1086/491745.
32. Kalt A, Schneider T, Ring S, Hoffmann J, Zeitz M, Stallmach A, et al. Decreased levels of interleukin-12p40 in the serum of patients with Whipple's disease. Int J Color Dis. 2006;21(2):114–20. https://doi.org/10.1007/s00384-005-0778-6.
33. Marth T, Neurath M, Cuccherini BA, Strober W. Defects of monocyte interleukin 12 production and humoral immunity in Whipple's disease. Gastroenterology. 1997;113(2):442–8. https://doi.org/10.1053/gast.1997.v113.pm9247462.
34. Desnues B, Raoult D, Mege J-L. IL-16 is critical for Tropheryma whipplei replication in Whipple's disease. J Immunol. 2005;175(7):4575–82. https://doi.org/10.4049/jimmunol.175.7.4575.
35. Ghigo E, Barry AO, Pretat L, Al Moussawi K, Desnues B, Capo C, et al. IL-16 promotes T. whipplei replication by inhibiting phagosome conversion and modulating macrophage activation. PLoS One. 2010;5(10):e13561. https://doi.org/10.1371/journal.pone.0013561.
36. Benoit M, Fenollar F, Raoult D, Mege JL. Increased levels of circulating IL-16 and apoptosis markers are related to the activity of Whipple's disease. PLoS One. 2007;2(6):e494. https://doi.org/10.1371/journal.pone.0000494.
37. Puéchal X. Whipple's arthritis. Joint Bone Spine. 2016;83(6):631–5. https://doi.org/10.1016/j.jbspin.2016.07.001.
38. James TN. On the wide spectrum of abnormalities in the coronary arteries of Whipple's disease. Coron Artery Dis. 2001;12(2):115–25. https://doi.org/10.1097/00019501-200103000-00005.
39. Marth T, Moos V, Müller C, Biagi F, Schneider T. Tropheryma whipplei infection and Whipple's disease. Lancet Infect Dis. 2016;16(3):e13–22. https://doi.org/10.1016/S1473-3099(15)00537-X.
40. Marth T, Raoult D. Whipple's disease. Lancet. 2003;361(9353):239–46. https://doi.org/10.1016/S0140-6736(03)12274-X.
41. Tarroch X, Vives P, Salas A, Moré J. Subcutaneous nodules in whipple's disease. J Cutan Pathol. 2001;28(7):368–70. https://doi.org/10.1034/j.1600-0560.2001.280706.x.
42. Walter R, Bachmann SP, Schaffner A, Rüegg R, Schoedon G. Bone marrow involvement in Whipple's disease: rarely reported, but really rare? Br J Haematol. 2001;112(3):677–9. https://doi.org/10.1046/j.1365-2141.2001.02648.x.
43. Louis ED, Lynch T, Kaufmann P, Fahn S, Odel J. Diagnostic guidelines in central nervous system Whipple's disease. Ann Neurol. 1996;40(4):561–8. https://doi.org/10.1002/ana.410400404.
44. Gerard A, Sarrot-Reynauld F, Liozon E, Cathebras P, Besson G, Robin C, et al. Neurologic presentation of Whipple disease: report of 12 cases and review of the literature. Medicine (Baltimore). 2002;81(6):443–57. https://doi.org/10.1097/00005792-200211000-00005.
45. Messori A, Di Bella P, Polonara G, Logullo F, Pauri P, Haghighipour R, et al. An unusual spinal presentation of Whipple disease. AJNR Am J Neuroradiol. 2001;22(5):1004–8.
46. Rusina R, Keller O, Síma R, Zámečník J. Peripheral neuropathy in Whipples disease: a case report. Cesk Patol. 2012;48(2):97–9.
47. von Herbay A, Otto HF, Stolte M, Borchard F, Kirchner T, Ditton H-J, et al. Epidemiology of Whipple's disease in Germany: analysis of 110 patients diagnosed in 1965–95. Scand J Gastroenterol. 1997;32(1):52–7. https://doi.org/10.3109/00365529709025063.
48. Matthews BR, Jones LK, Saad DA, Aksamit AJ, Josephs KA. Cerebellar ataxia and central nervous system whipple disease. Arch Neurol. 2005;62(4):618–20. https://doi.org/10.1001/archneur.62.4.618.
49. Mulroy E, Lynch T. Whipple's disease. In: Encyclopedia of the neurological sciences. Philadelphia: Elsevier; 2014. https://doi.org/10.1016/B978-0-12-385157-4.00367-5.

50. Schwartz MA, Selhorst JB, Ochs AL, Beck RW, Campbell WW, Harris JK, et al. Oculomasticatory myorhythmia: a unique movement disorder occurring in Whipple's disease. Ann Neurol. 1986;20(6):677–83. https://doi.org/10.1002/ana.410200605.
51. Simpson DA, Wishnow R, Gargulinski RB, Pawlak AM. Oculofacial-skeletal myorhythmia in central nervous system Whipple's disease: additional case and review of the literature. Mov Disord. 1995;10(2):195–200. https://doi.org/10.1002/mds.870100210.
52. Lynch T, Fahn S, Louis ED, Odel JG. Oculofacial-skeletal myorhythmia in Whipple's disease. Mov Disord. 1997;12(4):625–6.
53. Baizabal-Carvallo JF, Cardoso F, Jankovic J. Myorhythmia: phenomenology, etiology, and treatment. Mov Disord. 2015;30(2):171–9. https://doi.org/10.1002/mds.26093.
54. Black DF, Aksamit AJ, Morris JM. MR imaging of central nervous system Whipple disease: a 15-year review. Am J Neuroradiol. 2010;31(8):1493–7. https://doi.org/10.3174/ajnr.A2089.
55. Compain C, Sacre K, Puéchal X, Klein I, Vital-Durand D, Houeto J-L, et al. Central nervous system involvement in Whipple disease: clinical study of 18 patients and long-term follow-up. Medicine (Baltimore). 2013;92(6):324–30. https://doi.org/10.1097/MD.0000000000000010.
56. Frazier JL, Quinones-Hinojosa A. Isolated Whipple disease of the brain resembling a tumour. Acta Neurochir. 2009;151(2):173–5. https://doi.org/10.1007/s00701-008-0180-6.
57. Löhr M, Stenzel W, Plum G, Gross WP, Deckert M, Klug N. Whipple disease confined to the central nervous system presenting as a solitary frontal tumor: case report. J Neurosurg. 2004;101(2):336–9. https://doi.org/10.3171/jns.2004.101.2.0336.
58. Wroe SJ, Pires M, Harding B, Youl BD, Shorvon S. Whipple's disease confined to the CNS presenting with multiple intracerebral mass lesions. J Neurol Neurosurg Psychiatry. 1991;54(11):989–92. https://doi.org/10.1136/jnnp.54.11.989.
59. Schröter A, Brinkhoff J, Günthner-Lengsfeld T, Suerbaum S, Reiners K, Messmann H, et al. Whipple's disease presenting as an isolated lesion of the cervical spinal cord. Eur J Neurol. 2005;12(4):276–9. https://doi.org/10.1111/j.1468-1331.2004.01035.x.
60. Baisden BL, Lepidi H, Raoult D, Argani P, Yardley JH, Dumler JS. Diagnosis of Whipple disease by immunohistochemical analysis: a sensitive and specific method for the detection of Tropheryma whipplei (the Whipple bacillus) in paraffin-embedded tissue. Am J Clin Pathol. 2002;118(5):742–8. https://doi.org/10.1309/8YGR-FE7L-39LL-L37C.
61. Paulley JW. A case of Whipple's disease (intestinal lipodystrophy). Gastroenterology. 1952;22(1):128–33. https://doi.org/10.1016/S0016-5085(19)36367-X.
62. Keinath RD, Merrell DE, Vlietstra R, Dobbins WO. Antibiotic treatment and relapse in Whipple's disease. Gastroenterology. 1985;88(6):1867–73. https://doi.org/10.1016/0016-5085(85)90012-5.
63. Boulos A, Rolain JM, Mallet MN, Raoult D. Molecular evaluation of antibiotic susceptibility of Tropheryma whipplei in axenic medium. J Antimicrob Chemother. 2005;55(2):178–81. https://doi.org/10.1093/jac/dkh524.
64. Fenollar F, Perreal C, Raoult D. Tropheryma whipplei natural resistance to trimethoprim and sulphonamides in vitro. Int J Antimicrob Agents. 2014;43(4):388–90. https://doi.org/10.1016/j.ijantimicag.2014.01.015.
65. Fenollar F, Rolain J-M, Alric L, Papo T, Chauveheid M-P, van de Beek D, et al. Resistance to trimethoprim/sulfamethoxazole and Tropheryma whipplei. Int J Antimicrob Agents. 2009;34(3):255–9. https://doi.org/10.1016/j.ijantimicag.2009.02.014.
66. Feurle GE, Moos V, Schneider T, Fenollar F, Raoult D. The combination of chloroquine and minocycline, a therapeutic option in cerebrospinal infection of Whipple's disease refractory to treatment with ceftriaxone, meropenem and co-trimoxazole. J Antimicrob Chemother. 2012;67(5):1295–6. https://doi.org/10.1093/jac/dks008.
67. Fenollar F, Lagier J-C, Raoult D. Tropheryma whipplei and Whipple's disease. J Infect. 2014;69(2):103–12. https://doi.org/10.1016/j.jinf.2014.05.008.
68. Lagier J-C, Fenollar F, Lepidi H, Raoult D. Failure and relapse after treatment with trimethoprim/sulfamethoxazole in classic Whipple's disease. J Antimicrob Chemother. 2010;65(9):2005–12. https://doi.org/10.1093/jac/dkq263.

69. Ramzan NN, Loftus E, Burgart LJ, Rooney M, Batts KP, Wiesner RH, et al. Diagnosis and monitoring of Whipple disease by polymerase chain reaction. Ann Intern Med. 1997;126(7):520–7. https://doi.org/10.7326/0003-4819-126-7-199704010-00004.
70. Feurle GE, Moos V, Schinnerling K, Geelhaar A, Allers K, Biagi F, et al. The immune reconstitution inflammatory syndrome in Whipple disease. Ann Intern Med. 2010;153(11):710. https://doi.org/10.7326/0003-4819-153-11-201012070-00004.
71. Biagi F, Trotta L, Di Stefano M, Balduzzi D, Marchese A, Vattiato C, et al. Previous immunosuppressive therapy is a risk factor for immune reconstitution inflammatory syndrome in Whipple's disease. Digest Liver Dis. 2012;44(10):880–2. https://doi.org/10.1016/j.dld.2012.05.008.