Chapter 18
The Neurology of Whipple's Disease

Ribal Bassil and Carolina Ionete

Abstract Whipple's disease is a systemic illness caused by an infection with a bacterium of the *Actinomycetes* species called *Tropheryma whipplei*. The infection primarily causes gastroenteritis and malabsorption; however, it could also infect other target organs including the central nervous system (CNS). CNS involvement manifests as a wide spectrum of symptoms such as change in mental status, myoclonus, ophthalmoplegia, and ataxia. Whipple's disease is rare and mostly presents with nonspecific symptoms, therefore requiring a high clinical suspicion for prompt diagnosis. Early initiation of antibiotherapy could prevent bacterial dissemination and produce a complete resolution of symptoms.

Keywords *Tropheryma whipplei* • Whipple's disease • Central nervous system • Oculomasticatory myorhythmia • Oculofacial skeletal myorhythmia

Introduction

In 1907, George Hoyt Whipple, an American physician and Nobel Prize recipient, described a case of a 36-year-old physician who developed malabsorption with diarrhea, weight loss, and arthropathy and subsequently passed away 5 years later of complications of his disease. On autopsy, the identification of intestinal fat and lipid-burdened mononuclear cells prompted Whipple to call the disease "intestinal lipodystrophy."

Years later, further investigation of the disease revealed a systemic illness primarily affecting the gastrointestinal tract as well as other target organs including the heart, lungs, eyes, skin, and central nervous system (CNS). The disease became known as Whipple's disease in 1949 [1].

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Although Whipple's disease is best known for its systemic and gastrointestinal manifestations, neurological involvement is now very well recognized as either a complication of the systemic disorder or as primary presenting symptom.

Epidemiology

Whipple's disease is rare, making incidence and prevalence analyses range widely from one study to the other. It is most likely underdiagnosed given the nonspecific symptoms at the time of presentation and the absence of gastrointestinal involvement in many cases. Nevertheless, the available literature shows that Whipple's disease primarily affects middle-aged Caucasian men with 4:1 men to women ratio. The mean age of onset is around 50–55 years [2].

Etiology

While studying and staining tissues isolated from the gastrointestinal tract of the "intestinal lipodystrophy" case, George Hoyt Whipple interestingly described a "peculiar rod-shaped organism" that may or may not be associated with the etiology of the disease. More than 50 years later, a periodic acid-Schiff (PAS) weakly gram-positive bacillus was identified in the intestinal mucosa macrophages of similar cases [3, 4]. The organism was subsequently named *Tropheryma whippelii* (TW), with the name later changed to *Tropheryma whipplei*, following the successful tissue culture of the organism [5], although the previous nomenclature remains widely in use.

Tropheryma whipplei is ubiquitously expressed in the environment, including in the soil and in sewage water [6]. Furthermore, the organism has been isolated from the saliva and stool of clinically affected patients as well as healthy controls [7–9]. Taken together, this suggests both a genetic predisposition and environmental factors as important players in the bacterium pathogenesis. Although the evidence supporting a genetic predisposition to Whipple's disease is scarce, an association with HLA alleles DRB1*13 and DQB1*06 has been recently described [10].

To date, humans are the only known host for the bacterium. While exposure to the organism may be uneventful in some, in others it may lead to a self-limiting or chronic gastroenteritis that may progress to a chronic carrier or chronic disease state. Many cases with isolated non-gastrointestinal organ involvement have been described; however, it is hard to prove the absence of a preceding remote history of gastroenteritis at the time of the bacterium inoculation.

Given the predominant gastrointestinal manifestation of Whipple's disease and the organism detection in sewage water and stools, it is thought that *Tropheryma whipplei* is transmitted through the fecal-oral route. Although the bacterium has also been detected in human saliva, to date, there is no evidence of transmission via bodily fluids. Little is known regarding the modes of dissemination of the organism

once ingested; however the systemic and multi-organ involvement suggests a hematogenous and lymphatic spread.

Clinical Manifestations

Systemic Manifestations

Multiple organ systems could be affected in Whipple's disease either individually or in combination (Table 18.1). The list includes but is not limited to the gastrointestinal tract, lymphatics, musculoskeletal system, heart, lung, CNS, and, to a lesser extent, the peripheral nervous system (PNS).

A classical Whipple's disease clinical picture is a patient presenting with gastrointestinal and systemic involvement. The main presenting symptoms include diarrhea, abdominal cramping, and weight loss. Systemic symptoms are nonspecific and include fever, lymphadenopathy, and arthralgias. In many cases and in retrospect, arthralgias preceded the other manifestations and diagnosis by years [11–13]. If the disease remains untreated, chronic complications of malabsorption become

Table 18.1 Common clinical manifestations of Whipple's disease

Gastrointestinal
Diarrhea
Steatorrhea
Abdominal pain
Bloating
Malabsorption
Weight loss
Systemic
Fever
Lymphadenopathy
Arthropathy
Cardiac
Endocarditis
Pericarditis
Congestive heart failure
Pulmonary
Pleural effusion
Chest pain
Ocular
Uveitis
Keratitis
Retinitis
Papilledema

evident. Most noteworthy is vitamin D deficiency leading to osteomalacia and hyperpigmentation and vitamin B12 deficiency leading to anemia [14, 15].

Cardiac involvement is a well-recognized complication of Whipple's disease. In fact, in the right clinical setting, *Tropheryma whipplei* should be considered in the differential diagnosis of endocarditis, pericarditis, or congestive heart failure with initial negative workup [16–18].

Pulmonary manifestations could range from asymptomatic lymphadenopathy to dyspnea, chest pain, or pleural effusion [19].

Ocular involvement is not uncommon and mainly results in uveitis, although keratitis, retinitis, and optic neuritis have been described [20, 21].

Central Nervous System Manifestations

CNS infections result in small, sometimes confluent granulomas with preferential involvement of the cerebral cortical and deep gray matter. The granulomas consist of a PAS-positive macrophage core embedded within a large reactive astrocytic surface [22–24] (Fig. 18.1). It remains to be determined whether direct *Tropheryma*

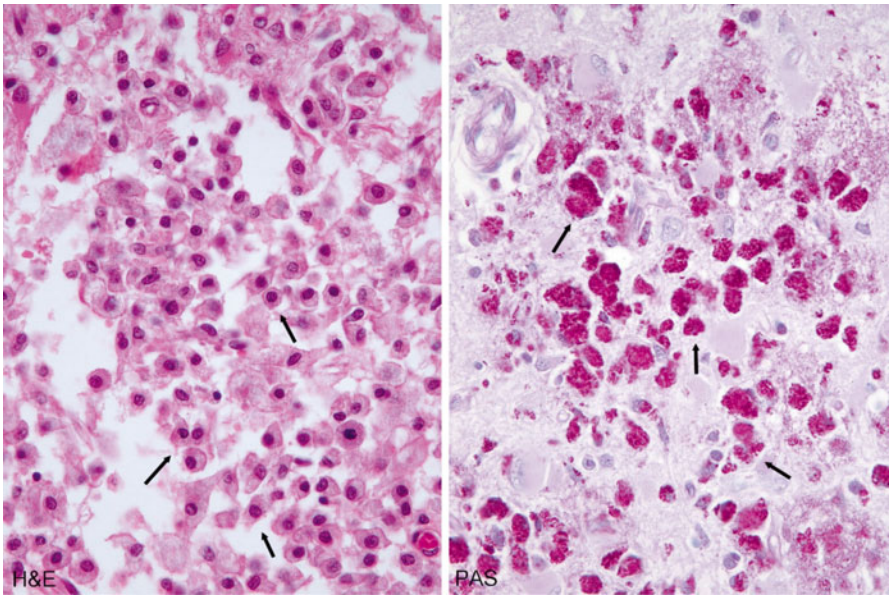

Fig. 18.1 A labeled composite image of the 40x images of CNS Whipple's disease. Autopsy specimen of the hippocampus from a 25-year-old male with a 1-year history of progressive dementia, supranuclear ophthalmoplegia, and right arm myoclonus. The H&E stain (*left image*) shows a large cluster of foamy macrophages (*arrows*) in the gray matter. The PAS stain (*right image*) shows PAS+ cytoplasmic inclusions consistent with *T. whipplei* bacteria within the macrophages (*arrows*). Original magnification, both images, 40× (Reproduced with permission from Dr. T Smith)

Table 18.2 Common CNS manifestations of Whipple's disease

Cerebral atrophy
Headache
Cognitive decline
Psychiatric signs
Myoclonus
Supranuclear gaze palsy
Autonomic dysfunction
Hypersomnia
Hyperphasia
OMM
OFSM
Aphasia
Dysarthria
Motor weakness
Paresis
Seizure
Ataxia
Nystagmus
Optic neuritis
Cranial nerve palsy

whipplei pathogenesis or the associated inflammatory granulomatous reaction, or both are responsible for the CNS pathology.

Neurological involvement may cause a wide spectrum of nonspecific signs and symptoms such as brain atrophy or headaches [13]. Some manifestations are more easily anatomically localizable depending on the underlying involved structures (Table 18.2).

Cognitive change is the most common neurological presentation and includes memory difficulty and behavioral changes. Nonspecific psychiatric manifestations are also common especially in the setting of cognitive decline [13, 25].

Vision could be compromised by direct ocular, optic nerve, or optic chiasm involvement. Furthermore, eye movement disorder should raise a high degree of suspicion for Whipple's disease, as it is the second most common presenting symptom. Ophthalmoplegia usually signals brainstem or cranial nerve involvement with supranuclear gaze palsy or vertical ophthalmoparesis [26–30].

Oculomasticatory myorhythmia (OMM) and oculofacial skeletal myorhythmia (OFSM) are rare ocular movement disorders that have not been associated with any pathology other than Whipple's disease [31, 32]. Although it is an uncommon presentation, it is considered pathognomonic of the disease. OMM consists of constant synchronous ocular pendular vergence oscillations with concurrent contractions of the masticatory muscles [33]. OFSM is similar to OMM in addition to synchronous rhythmic movements of the extremities and persists during sleep [34].

Focal cerebral involvement could result in symptoms such as dysarthria, aphasia, weakness, or paresis corresponding to the localization of the lesions [35]. Ataxia and nystagmus point to cerebellar involvement [36]. Cranial nerve palsies have also been reported [13].

Movement disorders include myoclonus or rarely Parkinsonism [34, 37, 38]. Seizures are most likely secondary to focal cortical lesions or limbic involvement [27, 39]. Autonomic dysfunction, hypersomnia, and hyperphagia signal hypothalamic involvement [34, 35, 40]. Large or confluent granulomas could present as space-occupying lesions exerting mass effect [41]. If obstructing the CSF circulation, hydrocephalus could be seen [42].

Myelopathy, either as isolated presentation or in concurrence with other CNS symptoms, has been described [30, 43, 44]. While Whipple's disease of the CNS is well established, PNS involvement is less common.

Diagnosis

Tropheryma whipplei has proven very difficult to culture [45]. Tissue biopsy and staining are impractical, especially in the setting of Whipple's disease with no gastrointestinal manifestation.

The diagnostic tool of choice is the isolation of a single bacterial 16S ribosomal RNA gene sequence by polymerase chain reaction (PCR) technique. In fact, it is the analysis of the bacterial gene by PCR that allowed the classification of the bacterium as novel *Actinomycetes* [46].

Saliva and stool sample PCR is not a reliable diagnostic study as it had been found to be positive in healthy individuals, presumed asymptomatic carriers [7, 8]. Therefore, the identification of the bacterium by PCR in the target organ is critical. Luckily, in the setting of CNS involvement, a tissue biopsy is rarely indicated, as CSF PCR is the cornerstone for diagnosis [44]. Of note, CSF fluid analysis could be unremarkable or it could demonstrate mildly elevated protein level or white blood cell count [13, 47].

Electroencephalography is non-diagnostic and usually shows generalized slowing or nonspecific findings corresponding to potential focal lesions [27].

Brain imaging studies such as CT scan or MRI are also nonspecific (Figs. 18.2 and 18.3). The findings range from normal brain to diffuse atrophy [13]. Lesions range from focal to scattered, contrast-enhancing or non-enhancing, and sometimes ring-enhancing lesion [30, 41]. Cases with space-occupying lesions complicated by hydrocephalus have been described [42, 48]. Spinal cord involvement has been reported; therefore, imaging would be indicated if the clinical presentation is suggestive of it.

Treatment

An infectious etiology of Whipple's disease has been proposed long before *Tropheryma whipplei* was identified; therefore, there is a well-documented history of successful antibiotherapy [49]. However, the emergence of many resistant or relapsing cases or subsequent presentations with neurological symptoms mandated a choice of antibiotics with excellent CNS penetration and good patients' tolerance [50].

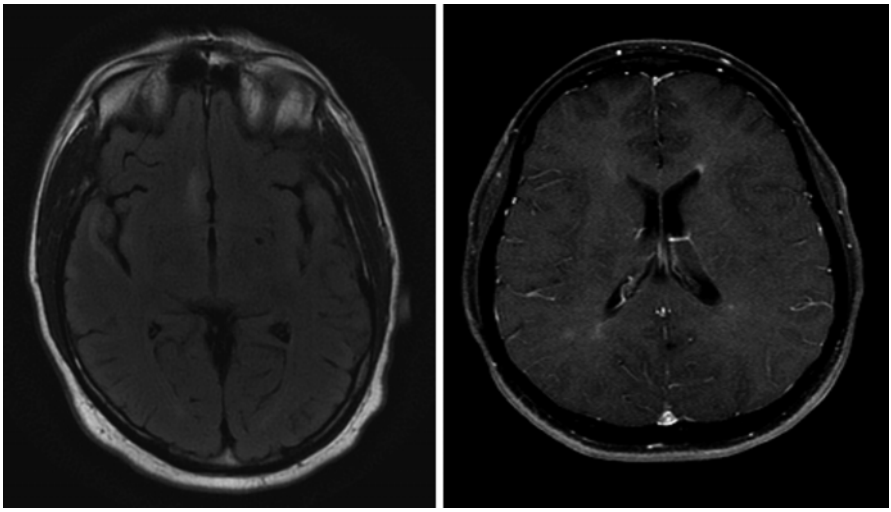

Fig. 18.2 Axial noncontrast FLAIR and axial T1 with gadolinium images demonstrate enhancing abnormally increased T2 signal intensity in the bilateral temporal lobe and right medial frontal lobe in a 45-year-old man presented with subacute rapid progressive dementia and biopsy proven Whipple's disease

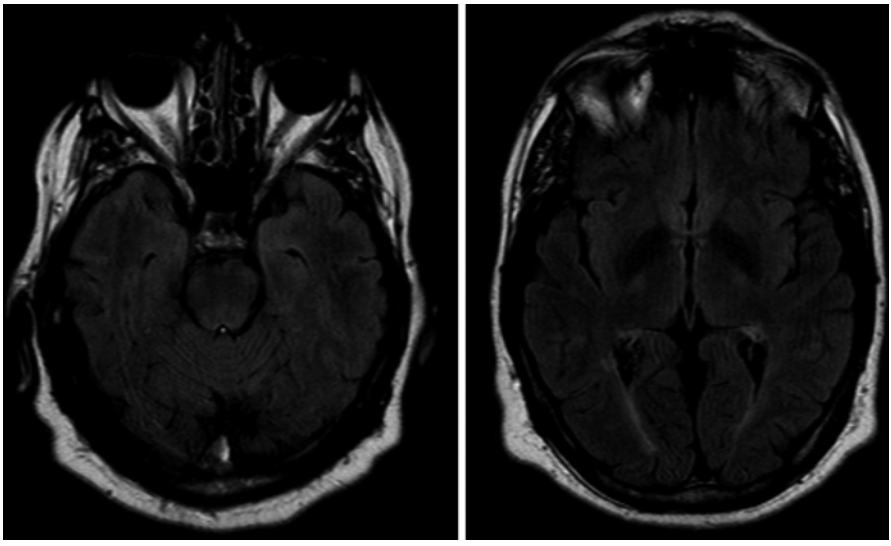

Fig. 18.3 Axial noncontrast FLAIR demonstrates abnormally increased T2 signal intensity in the bilateral medial temporal poles, pyramidal tracts (anterior aspect of the midbrain and internal capsule), and posterior midbrain involving periaqueductal region (quadrigeminal plate) in a 37-year-old woman, diagnosed by brain biopsy with Whipple's disease after she presented with oculomasticatory myokymia, vertical gaze palsy, and delirium

The treatment duration is not well defined; however, most studies show a preferable outcome with 2–4 weeks of intravenous agent administration, followed by 1 year of oral therapy. For patients with endocarditis or CNS infection, a longer 4-week course of intravenous antibiotherapy is recommended [51].

With regard to the choice of antibiotics and length of treatment, current guidelines recommend the administration of intravenous ceftriaxone at 2 g once daily for 2–4 weeks followed by oral trimethoprim-sulfamethoxazole (TMP-SMX) double-strength tablet twice daily for 1–2 years [52, 53]. Of note, several authors recommend ceftriaxone at 2 g twice a day during the parenteral treatment phase.

It would be prudent to have all patients receiving TMP-SMX on daily folic acid supplementation as TMP, a dihydrofolate reductase inhibitor, may cause folate deficiency.

For patients with penicillin or ceftriaxone allergies, the intravenous regimen is substituted with oral TMP-SMX double-strength tablet three times daily plus streptomycin at 1 g intramuscular daily for 2–4 weeks. For cases of sulfa drug allergy, oral TMP-SMX is substituted by oral doxycycline concurrently with hydroxychloroquine. Alternatively, oral cefixime has been used [51].

Prognosis

The use of antibiotics with excellent CNS penetration, both during the acute and chronic maintenance phases, has certainly improved outcomes and has decreased the recurrence rate. Overall, prognosis is good, especially in the absence of significant underlying target organ structural lesions. Clinical improvement is expected within weeks of initiation of therapy, and the success of therapy is judged based on clinical improvement.

Nevertheless, some cases of recurrence while on antibiotics or after completion of chronic therapy have been described. It is unclear whether this is related to host factors such as poor compliance or immune suppression or whether it is due to a change in the bacterial pathogenic or resistance profile. Therefore, in case of recurrence or failure of therapy, it is recommended that treatment should be reinstituted or the antibiotic regimen changed.

Although routine tissue or CSF PCR for *Tropheryma whipplei* has been considered, its value remains uncertain. However, in cases of recurrence or initial therapy failure, it would be reasonable to analyze the CSF or target tissue when feasible by PCR after completion of the antibiotic course and to determine the best course of action accordingly [54]. In fact, some authors advocate for lifetime prophylactic treatment following initial treatment failure [55].

Immune reconstitution inflammatory syndrome (IRIS) is the main complication following the initiation of treatment in Whipple's disease. This consists of a severe inflammatory process resulting in high-grade fever or other systemic symptoms. The population at risk includes patients previously on immunosuppressive treatment

or patients with Whipple's disease of the CNS [56]. If the reaction is severe enough, administration of corticosteroid therapy is indicated.

Conclusion

Timely diagnosis of Whipple's disease is challenging, as the presenting symptoms are highly variable and could virtually involve any organ system. Therefore, medical professionals of all specialties should be familiar with this diagnosis and keep a high clinical suspicion especially in the setting of atypical cases with negative initial workup. The prompt initiation of antibiotherapy has changed the natural course of this chronic, potentially life-threatening disease. However, routine follow-up is warranted as failure of therapy or disease recurrence has been well documented.

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