Whipple Disease of the Central Nervous System

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In 1907, George H. Whipple reported the clinical manifestations and autopsy findings for a patient with the disease that now bears his name [1]. Nearly all of the cardinal clinical manifestations of this disorder—including arthralgias, abdominal pain, fever, diarrhea, malabsorption, weight loss, and cough—were evident in this first patient reported. On the basis of observations of fat and fatty-acid deposits in the intestinal mucosa and mesenteric lymph nodes, Whipple termed the disease “intestinal lipodystrophy” and concluded that the subject of his case report suffered from a disorder of lipid metabolism. However, he did note small bacteria in silver-stained sections of mesenteric lymph nodes. Whipple made no mention of neurologic manifestations, and no postmortem examination of the central nervous system (CNS) was performed, yet it is now apparent that the CNS is a major site of involvement in extraintestinal Whipple disease (WD) [2, 3] (see below).

WD is a rare, chronic, and systemic illness characterized predominantly by intestinal involvement but including a variety of other organs, especially the lymphatic system, heart, and CNS [2]. It occurs predominantly in middle-aged men. Of 664 patients reviewed by Dobbins, men accounted for 86% of cases, with a mean age of 49 years [2]. The epidemiologic characteristics of WD of the CNS appear to be similar, although in 1 report there was no gender bias [4]. It is possible that CNS involvement reflects a different subset of patients, but this is unknown at present. WD appears to be very rare in children. Farmers are overrepresented among patients with this disorder [2].

WD is an infectious disease. As noted above, Whipple himself observed bacilliform bodies in involved tissues. Earlier studies had suggested a bacterial etiology, both because successful antibiotic treatment had been reported in 1952 [5] and because detection, by electron microscopy, of numerous small, uniform bacteria in involved tissues had been reported in 1961 [6, 7]. During the early 1990s, amplification of phylogenetically useful genetic sequences of microorganisms by techniques using 16S rRNA identified a unique bacterial 16S rDNA gene sequence in WD tissues [8, 9]. In addition, intact bacilli disappear with clinical response to antibiotics yet reappear during clinical relapse [10].

The WD bacillus has unusual morphology but appears to be monomorphic and undergoes binary fission in affected tissues. The bacillus is rod shaped, measures ~0.2 μm × 1.2 μm, and is surrounded by a 20-nm-thick cell wall. The outermost layer of this cell wall consists of a trilaminar membrane that resembles those of eukaryotic origin, whereas the inner, electron-dense layer of the cell wall reacts strongly with periodic acid-Schiff (PAS) reagents and thus accounts for the PAS staining pattern of bacilli and their remnants within macrophages [11]. The bacillus is weakly gram positive and is not acid fast. On the basis of the 16S rRNA gene sequences noted above, it has been suggested that the WD bacillus is a novel actinomycete, related to a number of other soil bacteria [8, 9]. A complete genome sequence of this bacillus was published earlier this year and strengthens the actinomycete hypothesis [12]. The proposed name is “Tropheryma whipplei” and is based on the Greek words trophe, for nourishment, and eryma, for barrier, because of the strong association between infection by this bacillus and malabsorption. The genome of this bacillus contains only 783 genes and is therefore unusually small for an actinomycete. Lack of genes for multiple critical biosynthetic and energy-producing pathways may be relevant to the difficulty of propagation of the bacillus in vitro. In addition, the genome contains a family of genes predicted to encode an unusual set of variable surface-associated proteins likely involved in pathogenesis and pathophysiology [3]. On the basis of the morphology and the other characteristics noted above, multiple attempts have been made to cultivate the WD bacillus in the laboratory; however, it was not until almost 100 years after the
first case report that this was accomplished, by Raoult et al., who, in 2000 [13], used a human fibroblast cell line inoculated with heart-valve tissue from a patient with WD, and culture-positive specimens have also now been extracted from duodenal tissue [14] and cerebrospinal fluid (CSF) (see below). The initial report of long-term cultivation suggested a bacterial doubling time of ~18 days, longer than that of any other previously characterized bacterium. Nevertheless, cultivation of the bacillus from CNS tissues has not previously been reported, and multiple fundamental questions regarding the pathogenesis and pathophysiology of WD of the CNS remain unanswered [3].

In this issue of the Journal, Maiwald et al., from Stanford University and the University of Heidelberg (Germany), report the first cultivation of Tropheryma whipplei from CSF [15]. This finding is noteworthy, as are several other aspects of their report, which are outlined below. Furthermore, their conclusions are sound, and the implications are numerous.

The cultivation of T. whipplei from CSF, as documented by Maiwald et al. in their report in this issue of the Journal, suggests that the pathology characteristic of WD of the CNS may be mediated, at least in part, by local bacterial replication. Nevertheless, the exact incidence of CNS involvement in patients with WD remains unknown, and many aspects of the pathogenesis and pathophysiology of WD of the CNS are poorly understood [3]. Clinical manifestations suggesting CNS involvement are prominent in up to 43% of patients with WD who have been reported in the literature [2], but only ~5% of patients present with manifestations in the CNS alone [4]. The frequency of CNS involvement may be much higher, however. The characteristic pathology of WD of the CNS was reported in 1936, although it was >50 years later, after reexamination by a variety of histologic techniques, that this patient was correctly classified as presenting a case of WD [16]. Thorough studies of the pathology of WD of the CNS did not begin to appear until the 1960s. In a series of patients reported by Enzinger and Helwig, characteristic brain lesions associated with this disorder were demonstrated in 10 of 11 cases subjected to postmortem examination [17]. Furthermore, with the advent of polymerase chain reaction (PCR) technology, either the WD bacillus or its components were detected in the CSF of 7 of 10 cases before therapy and in 3 of 11 cases after therapy [18]. It is worth noting that both cases described by Maiwald et al. in their report in this issue of the Journal were asymptomatic with respect to CNS manifestations and that, despite remission of intestinal WD, 1 of them had a cultivatable bacillus >1 year after an appropriate course of therapy. Thus, it is probable that the CNS is a frequent, perhaps even universal, site of involvement in extraintestinal WD. Some have argued that the frequent use of antimicrobial agents, which is prevalent in our society, may suppress subclinical or overlooked WD of the intestine, only to become manifest in the CNS later. The implications for therapy could be profound (see below).

In cases of WD of the CNS, bacilli were first seen in the brain in 1969, with the aid of electron microscopy [19]. The bacillus undergoes binary fission, and this suggests that active bacterial replication is important in the pathophysiology of WD, a suggestion corroborated by the identification of CSF cultures that are positive for WD. The characteristic pathology of WD of the CNS, with prominent involvement in a perivascular and subependymal distribution, suggests hematogenous dissemination. Nevertheless, the mechanisms by which this agent traverses the blood/brain barrier and escapes host defense mechanisms remain unknown. As is documented by Maiwald et al. in their report in this issue of the Journal, the bacillus displays both extra- and intracellular forms during growth in vitro. These forms have also been documented in infected brain tissue. Extracellular bacilli may either enter the CNS by as-yet-unknown mechanisms or, during normal trafficking patterns, be carried, within circulating monocytes, intracellularly, into the CNS. It is important to note that both the contribution that the bacillus itself makes to the manifestations of WD of the CNS and the host response to the presence of the bacillus remain unknown and have obvious prognostic implications. In cases characterized by extensive CNS involvement, bacilli are found in neurons as well as in macrophages, and neuronal loss with reactive astrocytosis has been documented [3]. This finding has implications for the reversibility of CNS manifestations in those patients with WD who are symptomatic, reversibility that, even in the presence of intensive antimicrobial therapy, often is suboptimal.

There is no doubt that Maiwald et al. have isolated the agent of WD in 2 patients whom they discuss in their report in this issue of the Journal. They used a variety of techniques, including PCR, in situ hybridization, PCR internal standards (i.e., "mimics"), and scanning and transmission electron microscopy. Their report is the first to provide definitive quantitative measurement of T. whipplei growth in vitro and to correlate, in identical specimens, in situ hybridization and both bacterial morphology and the 16S rRNA sequence of T. whipplei. It seems certain that the fibroblast cultures were not contaminated with other bacteria. In their report in this issue of the Journal, Maiwald et al., on the basis of extensive propagation in vitro, estimated that the doubling time of the strains from their CSF specimens was 4 days, which differs from the 18 days reported in an earlier study [13] but is still very long for a bacterium. These differences are likely methodological, since the fibroblast cell line, the media, the percentage of fetal calf serum used after confluence was reached, the inoculum, and the frequency of media changes all differed from those reported elsewhere by Raoult et al. [13]. In a more recent study, by a group in Marseille, who employed molecular techniques to study antibiotic susceptibility of T. whipplei, the doubling time
for the 3 strains examined was estimated to be 32–48 h [20]. Although these doubling times are shorter than those reported by Maiwald et al. in their report in this issue of the Journal, it is obvious that T. whipplei divides slowly under the in vitro conditions studied thus far and that this may have important implications for antimicrobial therapy.

The diagnosis of WD of the CNS remains challenging. Most such cases have been inferred when a patient with documented WD outside the CNS presents with CNS manifestations and abnormalities identified by neuroradiologic tests or analysis of CSF. Brain biopsies are rarely useful or necessary, since the focal nature of the pathologic process often produces false-negative results. CSF may either be normal or display mildly elevated protein and/or a modest pleocytosis. CSF glucose is almost uniformly normal [2]. When the results of PAS staining of cell pellets obtained by cytocentrifugation of CSF samples are positive, there is strong presumptive evidence of CNS involvement by T. whipplei [21]. However, the PAS stain may be positive with other microorganisms, such as Histoplasma capsulatum or Mycobacterium avian complex. The PCR assay for the causative agent of WD is highly sensitive and specific and provides direct evidence of CNS involvement when CSF samples are positive. Furthermore, PCR may detect the bacillus in duodenal mucosa, even in the absence of intestinal manifestations, in patients with extraintestinal WD. Nevertheless, PCR-based diagnostic tests for WD have not been rigidly standardized and are not widely available. Serologic tests based on antigens obtained from cultivated bacteria, as well as in situ immunohistochemical approaches, may be valuable in the future [3].

As stated above, 1 of the patients studied by Maiwald et al. in their report in this issue of the Journal yielded a CSF culture positive for T. whipplei, despite 1 year of recommended antimicrobial therapy, a finding that is analogous to the positive PCR results in spinal fluid obtained by other investigators even after therapy. The optimal regimen for the treatment of WD of the CNS remains undefined. Nevertheless, because of the characteristic paucity of inflammation of the pathology found in the brains of patients with WD, as well as the mild abnormalities detected by the analysis of CSF in documented cases, penetration of selected drugs across a relatively intact blood/brain barrier must be a primary consideration. Thus, it is somewhat surprising that most experts continue to recommend a penicillin and an aminoglycoside for the initial 14 days of therapy for WD at any site. Both agents would be expected to penetrate an intact blood/brain barrier poorly. Trimethoprim-sulfamethoxazole at a dose of 1 double-strength tablet 2–3 times daily for ≥1 year has become the standard therapy for patients with WD [2, 3], and both agents in the combination do penetrate the blood/brain barrier adequately, even in the absence of intense inflammation. Other agents—including chloramphenicol, ceftriaxone, cefixime, and selected fluoroquinolones—have been used in small numbers of patients with WD of the CNS [3]. Molecular evaluation of antibiotic susceptibility, by measurement of the inhibition of DNA copy-number increase, by real-time quantitative PCR, has documented differences even among the quinolones (e.g., levofloxacin is more active than ciprofloxacin) [20]. At present, the duration of therapy is largely empirically determined; however, PCR-based detection of persistent T. whipplei DNA could be useful in therapeutic decisions regarding the duration of therapy and/or its reinstitution after presumed relapse. Some authorities recommend that antibiotic therapy for WD of the CNS be continued for 2 years and perhaps indefinitely. The use of PCR methodology may allow a more formal recommendation regarding the duration of therapy in the future. Despite uncertainties regarding the actual role of the WD bacillus versus the host inflammatory response in CNS pathology, corticosteroids cannot be recommended, since, as has been reported in a recent review, these agents have been associated with progression of WD and/or with death [4]. Given the frequent occurrence of macrophages in pathologic lesions characteristic of WD, it is perhaps surprising that more cases have not been described among immunosuppressed patients. WD has been described in patients with AIDS [22], but, again, the proper antimicrobial regimen and duration of therapy remain unknown. Unfortunately, regardless of the regimen, the degree of clinical improvement is often disappointing.

The findings outlined by Maiwald et al. in their report in this issue of the Journal are noteworthy, as has been noted above; however, like the findings of any good study, they raise many more questions, especially with regard to the pathogenesis, pathophysiology, diagnosis, monitoring, and treatment of WD of the CNS. Finally, and most important, further characterization of cultivation-resistant bacterial pathogens, as exemplified by T. whipplei as a paradigm, may yield significant new information on other chronic conditions that currently are considered to be “idiopathic.”

References

7. Yardley JH, Hendrix TR. Combined electron