



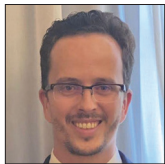
Review Article

Isolated central nervous system Whipple disease

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ABSTRACT

Background: Whipple disease (WD) is an infection caused by *Tropheryma whipplei*, which might present in three different forms: classical, localized, and isolated in the central nervous system (CNS).

Methods: We report the result of a systematic review of the literature on WD unusually presenting with exclusively neurological symptoms, including two previously unpublished cases. A description of two cases with isolated CNS WD was performed, as well as a literature search in *Cochrane*, *Scielo*, and *PubMed*.

Results: Two male adult patients presented with exclusively neurological symptomatology. Both magnetic resonance imaging (MRI) showed an intracranial mass suggestive of brain tumor. The histopathological examination was consistent with WD, with no systemic involvement. In the review of the literature, 35 cases of isolated CNS WD were retrieved. The median age at diagnosis was 43.5 (IQR 31.5–51.5). In 13 patients, the MRI showed a brain mass consistent with a brain tumor. The most common finding in the biopsy was the periodic-acid Schiff-stained foamy macrophages. Only five cases presented the pathognomonic sign of oculomasticatory myorhythmia. Thirteen cases had an adverse outcome that resulted in death during follow-up, whereas another 13 improved. The other nine patients remained stable or presented moderate improvement.

Conclusion: Isolated CNS WD is a rare disease that should be considered among the differential diagnosis of CNS mass lesions. Brain biopsy is necessary to establish the diagnosis. It is stressed in the literature that an extended antibiotic course is required to prevent relapses and to control the disease.

Keywords: Brain tumor, Cerebral mass, Infection, *Tropheryma whipplei*, Whipple disease

INTRODUCTION

The central nervous system (CNS) in Whipple disease (WD) might be involved in three different situations: CNS involvement in classic WD, CNS relapse in previously treated WD, and isolated CNS infection.^[6] Polymerase chain reaction (PCR) on cerebrospinal fluid (CSF) for *Tropheryma whipplei* is a major tool for diagnosis and may be positive in the absence of meningitis (The infection is caused by the soil-borne Gram-positive bacillus *T. whipplei*).^[6] Relman *et al.* identified the bacterium as an actinomycete.^[50]

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T. whipplei-infected macrophages contain particles that stain positive with periodic acid-Schiff (PAS).^[26] Immunocytochemistry with specific antibodies against *T. whipplei* may also be used. PCR analysis can be performed and is followed by sequencing the amplified product. Fluorescence *in situ* hybridization in tissue specimens and *T. whipplei* culture on human fibroblast cell lines may also be performed in specialized laboratories.^[6] It is important to note that a negative PCR from a CSF sample does not rule out WD in the setting of isolated intracranial disease.^[20] In a review of cases of isolated intracranial disease, CSF PCR for *T. whipplei* was positive in only two out of seven patients.^[42] EEG has been reported to show nonspecific slow wave activity and abolition of sleep-wake cycles.^[27]

MATERIALS AND METHODS

Besides describing two previously unpublished cases of WD presenting with focal brain lesions, a systematic review of the literature was conducted to identify all reported cases of WD presenting with exclusively CNS lesions, which were identified in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), Cochrane (<https://www.cochrane.org/es/evidence>), and Scielo (<https://scielo.org/es/>) databases.

The following search strategy was used “(WD or *T. whipplei*) AND (Central Nervous System OR CNS) AND (brain OR mass).” In Scielo search tool, the research was limited to abstract, keywords, and title, while no restriction was included in PubMed search tool.

Selection: The authors screened articles found by electronic search and evaluated their appropriateness based on title and abstract according to the established criteria. Articles were selected if they reported original data on laboratory confirmed WD cases presenting with brain focal lesions detected by any diagnostic tool (computed tomography [CT] scan, magnetic resonance imaging [MRI], CT Positron emission tomography, and lumbar puncture). Exclusion criteria were: (1) studies concerning WD with gastrointestinal or systemic disease; (2) *in vitro* studies; (3) basic research; (4) articles with full text written in languages other than that of at least one of the members of the team could read and understand (namely English, French, and Spanish); (5) only radiological findings or descriptions; and (6) spinal affection. If the eligibility of the documents could not be ascertained according to the abstract and title only, the full text was analyzed to exclude or include the document. The reference lists of all included articles were systematically reviewed for additional relevant documents to add.

Two cases

Case 1

A 51-year-old man was admitted because of dysnomia, blurred vision, and gait instability for the previous 3 days. Two months before admission, he noticed semantic paraphasias, a

right visual field defect and difficulty in concentration. His previous medical history was remarkable for type I *diabetes mellitus* since he was 22 years old and hypercholesterolemia. He had been diagnosed with idiopathic hypersomnia and suffered from Achilles tendonitis in 2015. He received follow-up for an isolated pulmonary nodule. He was otherwise healthy and fulfilled a Mediterranean diet. The patient is a musician, so reading sheet music and composing new pieces posed a hard task. He never had fever nor bowel problems, but he had suffered from an irritative cough for the past year. He had travelled to the United States of America 10 years ago and to Portugal the previous year. He was receiving the following treatment: insulin, simvastatin, and salbutamol.

An MRI was then performed [Figure 1], showing a left, solid, infiltrating, expansive, temporoparietal 4 cm mass, suggestive of periventricular glial tumor. Perfusion studies showed that the image was consistent with a low-grade glioma; however, it had an intense contrast enhancing and a very low ADC value.

His neurological examination was remarkable for a motor language blockade with phonemic paraphasias and a right homonymous quadrantanopia. He did not improve with corticosteroid therapy. A full body computed tomography was performed to rule out a possible primary tumor, this being normal.

Surgical resection with craniotomy was then recommended with the presumptive diagnosis of glioblastoma. He was not considered to be a good candidate for awake brain surgery due to his language dysfunction.

The patient underwent brain biopsy and remained well with no new deficits after the procedure.

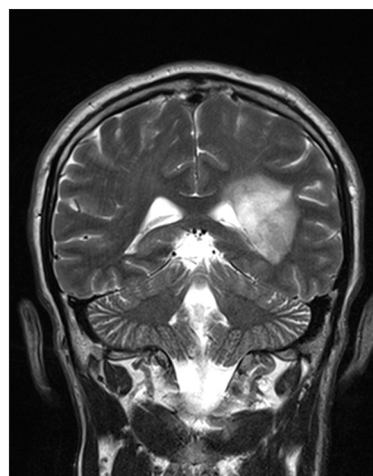


Figure 1: Coronal section of a magnetic resonance imaging showing a left, solid, infiltrating, expansive, temporoparietal 4 cm mass, suggestive of a periventricular glial tumor.

He was discharged and followed up at the outpatient department awaiting a definitive diagnosis.

Histopathological examination showed foamy histiocitary infiltration with intense PAS positive granular and rod-like cytoplasmic material, suggestive of WD [Figure 2]. The remaining biopsy piece was then recovered to perform a specific PCR for *T. whipplei*; unfortunately, the result was negative, probably due to sample artefaction after paraffin inclusion-subsequent deparaffinization.

According to Louis 1996 diagnostic criteria, he was diagnosed of WD with exclusive CNS involvement. Antibiotic therapy was then started with intravenous ceftriaxone and cotrimoxazole P.O. for a year.^[36]

In the outpatient follow-up, his language and visual field improved. He only had occasional headaches. In the first 6-month follow-up, the MRI also showed an improvement with a decreased size and mass effect as well as a loss of contrast-enhancement. He was then assessed in the rehabilitation outpatient clinic, with no significant language dysfunction but an ejective dysfunction with difficulty in maintaining concentration and work memory. His auditive comprehension capabilities, planification, social chatting, and daily activities were affected. In his last MRI, there was a stable white matter lesion, left paraventricular in location, residual to an inflammatory lesion due to WD, and with slight enlargement of the adjacent atrium. There was no contrast-enhancement.

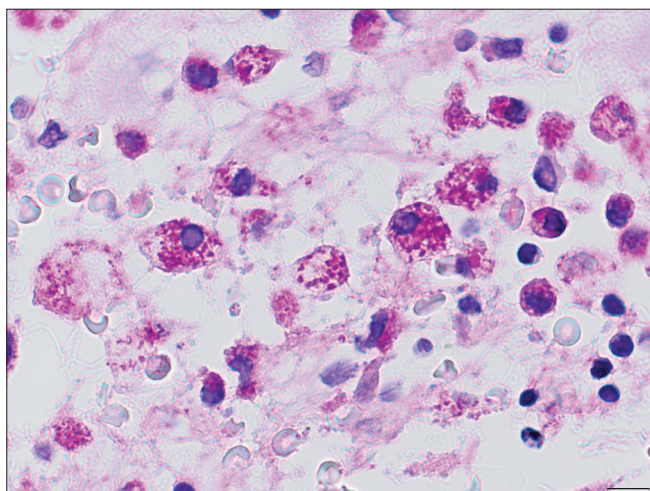


Figure 2: ×100 magnification. The samples were composed mainly by white matter and revealed an extensive infiltration by many perivascular foamy histiocytes which were immunoreactive for CD68 and CD163 and showed excentric, large, and “bean-like” nucleus within a wide, granular, and eosinophilic cytoplasm. PAS staining revealed intense and granular staining in the cytoplasm of the histiocytes. Zhiel staining was negative. Other findings of relevance were the presence of gliosis and small clusters of mature lymphocytes. No signs of malignancy were found.

After 2-year follow-up, the patient remains well; he has now resumed his previous job as a music teacher. The main symptom he notices is the difficulty in composing new pieces of music.

He is progressively regaining his usual activities (musical composition) although he feels a bit insecure. He still occasionally gets confused with words. In this case, respecting the patient’s autonomy principle in preferring to undertake biopsy has permitted to reach the diagnosis with a low probability of sequelae.

Case 2

A 78-year-old-patient was referred because of a 4-day history of weakness in his left side that was most prominent in the left inferior limb. No sensitive, language, or visual defects were found in the physical examination. His medical history was remarkable for rheumatoid arthritis, and he was receiving chronic treatment with salazopyrine at a daily dose of 2 g.

A CT scan of the brain showed a mass located in the deep white matter of the right frontal lobe, which was suggestive of metastases. Sequences of perfusion in the MRI demonstrated that the focal mass in the white matter of right precentral corona radiata behaved like an inflammatory lesion.

A brain biopsy was performed; an interstitial histocyte infiltration at white matter and cortex was evident with microgranuloma formation and no necrosis, as well as bacillar cytoplasmic structures that were all consistent with WD.

No alterations were found in body computed tomography, upper and lower tract endoscopies, lumbar puncture, or multiplex PCR for CNS pathogens.

He received intravenous treatment with daily ceftriaxone for a month, and then cotrimoxazole 800/160 mg orally every 12 h for 1 year. At 2-year follow-up, the patient has partially recovered strength in his left lower limb and remains stable up to date, with significant improvement in MRI.

DISCUSSION

In about 5% of all patients with WD, the disease is isolated or primary.^[3]

WD is most likely to affect Caucasian middle-aged (the median age at diagnosis was 43.5 [IQR 31.5–51.5]) men (8 men: 1 woman) who live in rural areas (20) and are human leukocyte antigen-B27-positive.^[3,12,18]

The bacterium has been isolated in duodenal (4.8%) and gastric (11.4%) biopsies of healthy carriers suggesting that it might be a commensal organism.^[53] Underlying immunosuppression or immune dysfunction is an important predisposing factor for WD.^[15,31,39,41]

Reduced pro-inflammatory cytokines associated with inflammatory macrophages have been implicated in the establishment of *T. whipplei* in the host.^[41,43,44] In addition to underlying immune dysfunction, pathogen-mediated dysregulation of macrophage activation also appears to play a role in pathogenesis.^[20]

Exclusive confinement to the CNS is extremely rare.^[55] In these cases, the development of an isolated cerebral mass is exceptional.^[35] Humans are the only known host for the infection.^[15,36,37]

In a small study by Compain *et al.*, mild weight loss in isolated CNS WD was described, as well as distinct patterns of brain MRI lesions: normal,^[54] diffuse, and focal lesions.^[6] WD rarely presents with isolated neurologic involvement (4–8%).^[6,42] The average time to WD diagnosis was 24 months. However, the delay was only 2 months in patients with pseudotumoral brain lesions.^[6] A study carried out in 2011 showed that progressive dementia and ataxia were significantly more frequent in patients with isolated *T. whipplei* encephalitis than in patients with classic WD with neurologic involvement.^[6,14] The lack of significant weight loss, a common manifestation of classic WD, is consistent with the absence of digestive involvement. Otherwise, a focal tumor-like brain lesion is a rare presentation of CNS WD.^[14,42]

The symptoms of cerebral WD include oculomotor abnormalities,^[29] ataxia,^[45] seizures,^[24] psychiatric disturbances,^[11] dementia,^[47] and aseptic meningitis.^[3] These neurological symptoms are varied^[56] and often complex but oculomasticatory myorhythmia (OMM) and oculo-facioskeletal myorhythmia are pathognomonic of CNS WD.^[36,37]

The most reported CNS symptoms are cognitive changes, affecting 71% of patients with CNS manifestations.^[13] Among other frequently reported complications are supranuclear ophthalmoplegia (in 51% of patients), impaired mental status^[22] (50%), hypothalamic manifestations^[46] (31%), myoclonic movements^[25] (25%), and ataxia (20%).^[13] About 20% of patients with CNS involvement have oculomasticatory or oculo-facioskeletal myorhythmia.^[13] Only roughly 10% of patients with CNS WD develop the classic CNS triad of dementia, supranuclear ophthalmoparesis, and movement disorder (most often myoclonus or oculomasticatory or oculo-facioskeletal myorhythmia).^[3]

The brain lesions detected by computed tomography and MRI are particularly heterogeneous:^[38] brain atrophy, contrast-enhancing space-occupying lesions,^[49] white matter lesions,^[10] ring-enhancing lesions,^[8] and hydrocephalus.^[1] CSF analysis may show differences ranging from a normal result to pleocytosis and elevated protein count level.^[1]

MR imaging of neuroWD may be diverse,^[59] but several features including early involvement of mediobasal structures

as well as preference of lesions for deep and periventricular areas along with ependymal involvement are highly suggestive.^[5] These areas are also involved in sarcoidosis, Behçet's disease, and lymphoproliferative diseases.^[5]

Louis *et al.* (1996) proposed diagnostic criteria for CNS WD. They consider a definite diagnosis if a patient meets at least one of three criteria:^[36]

- OMM or oculo-facioskeletal myorhythmia
- A positive CNS tissue biopsy or a positive biopsy of another tissue associated with neurologic signs consistent with WD^[40]
- A positive PCR tissue.

Even though CNS WD is rare and challenging to diagnose,^[48] it is being recognized with increasing frequency because of a greater awareness, better diagnostic tools, and possibly a true increase in incidence.^[14,15] We have tried to emphasize the need for a high index of suspicion for this disease, as the differential diagnosis is extensive and clinical and radiologic data usually give only poor diagnostic hints.^[30]

According to Delarbre *et al.*, *T. whipplei* infection should be considered in the absence of clinical response or in case of worsening of inflammatory rheumatism under tumor necrosis factor inhibitor treatment, especially in case of atypical features.^[9]

In the absence of PCR positivity, it is not possible to make a definitive isolated WD diagnosis. Although, supportive findings including the presence of rapidly progressive encephalitis^[28] plus ataxia; involvement of mediobasal structures on MRI;^[2] PAS positivity of brain biopsy specimen; exclusion of other infectious agents and malignant diseases with rigorous testing; and positive response to antibiotic treatment lead to the diagnosis of possible isolated CNS WD.^[57]

Fenollar *et al.* proposed a classification system for chronic Whipple's encephalitis patients. According to this system, patients with positive PCR of CSF and/or brain biopsy are regarded to have definite CNS WD and with positive staining of PAS and electron microscopy of brain biopsy is regarded to have possible isolated cerebral WD.^[51]

Although there are no clear guidelines about the best first line therapy, one group with some of the most extensive clinical experience in the treatment of Whipple's endocarditis recommends a combination of doxycycline plus hydroxychloroquine for treatment, which is the only bactericidal regimen in a tissue culture.^[15] Compain *et al.* also suggested that the combination of doxycycline and hydroxychloroquine is more efficient.^[6] Ceftriaxone followed by cotrimoxazole represents an alternative option for therapy.

To clear *T. whipplei* from the CNS, patients need primary treatment for 2 weeks with antibiotics that attain high CSF levels (e.g., ceftriaxone or penicillin G), followed by oral cotrimoxazole for 12 months.^[16,21] Patients should be followed

for at least 10 years, as many develop late recurrences that can severely injure the CNS.^[21]

Since CNS relapses carry a poor prognosis, antibiotics should not be reduced or discontinued. They should be prescribed at least for 1 year to prevent relapses.^[23]

The rate of relapse is particularly high with tetracycline (up to 35%) and one of the cases of chronically relapsing CNS Whipple's was successfully treated with recombinant interferon along with conventional antibiotics.^[39,52]

Several articles commented on the efficacy of trimethoprim-sulfamethoxazole and initial ceftriaxone treatment.^[16,17] However, recent articles mention failures and relapses after trimethoprim-sulfamethoxazole treatment.^[32,33] This is attributed to a possible trimethoprim-sulfamethoxazole resistance, which was demonstrated *in vitro*.^[4,32] Due to these findings, the current recommendations suggest a bactericidal treatment with a combination of both doxycycline plus hydroxychloroquine.^[32] To the best of our knowledge, no studies are available on the proper duration of antibiotic treatment.^[39] Apart from trimethoprim-sulfamethoxazole resistance, another possible cause of relapse in WD patients is the immune reconstitution inflammatory syndrome. Transient clinical worsening, attributable to immune reconstitution syndrome, may occur in the early months of treatment.^[6] This syndrome was first described in HIV-infected patients after initiation of antiretroviral therapy and later was observed in patients with leprosy and tuberculosis. It was also proven in patients with WD.^[18,19] If this was the case, the patient could benefit from adjuvant corticosteroid therapy; thalidomide efficiency has also been described.^[34]

In our review of the literature, we have found 35 cases of isolated CNS WD. They were published between 1975 and 2017. Twenty-two of them were men and 13 women. The mean age was 42 years old with a median of 43 years old. The most common signs and symptoms were cognitive impairment and memory loss, ataxia, seizures, cranial nerve palsies, nausea, behavioral change, headache, sleep disturbances,^[7] and language alterations. Only five of the cases had the pathognomonic sign of OMM. Thirteen of the patients presented like a brain tumor in the MRI. Other presumptive diagnosis was infectious or inflammatory processes, epilepsy, and dementia. The usual initial approaches were surgery, biopsy, antiepileptics, or antibiotics. The most common diagnostic clue in the brain pathology was the PAS+ macrophages. Thirteen of the cases were dead in the follow-up while another 13 improved. The other nine patients had little improvement or were stable.

CONCLUSION

In the differential diagnosis of glioblastoma, we should consider anaplastic astrocytoma, toxoplasmosis, cavernoma,

cerebral abscess, CNS lymphoma, encephalitis, intracranial hemorrhage, metastasis, oligodendroglioma, radionecrosis, and WD.

Isolated CNS WD is a clinical challenge and should be considered in the differential diagnosis in unusual cases of encephalitis. Brain biopsy is necessary to establish the diagnosis of isolated CNS WD. It is stressed in the literature that an extended antibiotic course is required to prevent relapses and to control the disease.^[58] As the exact treatment duration of CNS-WD has not been established, patients should be closely followed in case of antibiotics discontinuation to monitor for potential relapse, especially in case of coexisting immunosuppression.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Nil.

Conflict of interest

There are no conflicts of Interest.

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