

WHIPPLE'S DISEASE WITH NEUROLOGICAL MANIFESTATIONS

Case report

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ABSTRACT - Whipple's disease (WD) is an uncommon multisystem condition caused by the bacillus *Tropheryma whippelii*. Central nervous system involvement is a classical feature of the disease observed in 20 to 40% of the patients. We report the case of a 62 years old man with WD that developed neurological manifestations during its course, and discuss the most usual signs and symptoms focusing on recent diagnostic criteria and novel treatment regimens.

KEY WORDS: Whipple's disease, inflammatory bowel disease, dementia, polyneuropathy.

Doença de Whipple com manifestações neurológicas: relato de caso

RESUMO - A doença de Whipple (DW) é distúrbio multissistêmico raro causado pelo bacilo *Tropheryma whippelii*. O envolvimento do sistema nervoso central é um aspecto clássico da doença, sendo observado em 20 a 40% dos pacientes. Relatamos o caso de homem de 62 anos com DW que desenvolveu manifestações neurológicas durante sua evolução, com o objetivo de discutir os sinais e sintomas mais comuns e destacar os critérios diagnósticos e propostas terapêuticas mais recentes.

PALAVRAS-CHAVE: doença de Whipple, doença inflamatória intestinal, demência, polineuropatia

Whipple's disease (WD) or intestinal lipodystrophy was first described in 1907¹. It is a relatively rare multisystem disorder caused by the gram-positive bacillus *Tropheryma whippelii*. The usual presenting complaints include pronounced weight loss, mal-absorptive diarrhea (sometimes accompanied by abdominal cramping and bloody stool), recurrent non-deforming polyarthritides and longstanding low grade fever². Cutaneous hyperpigmentation and lymphadenopathy are also common clinical signs. Central nervous system (CNS) involvement is a classical feature of WD observed in 20 to 40% of cases. CNS manifestations are myriad and usually develop in later stages of the illness³, often with cranial nerve and cognitive complaints. Approximately 5% of the patients follow an unusual presentation with isolated CNS symptoms⁴.

Available data on CNS WD are scant, consisting basically of isolated case reports. Gerard et al.³ found only 122 reported cases in the literature since 1960, most of them in Europe and

North America. To our knowledge, the following case is the first to be reported in Brazil.

CASE

A 62-year-old white man, retired electrician, came to our Gastroenterologic Clinic in 1989 complaining of increased stool frequency and liquidity, associated with pronounced weight loss (20 Kg) in the last 2 years. Subsequent investigation disclosed a mal-absorptive syndrome, steatorrhea and hepatosplenomegaly. Six months later, he developed bilateral knee arthritis which subsided spontaneously in two weeks. In 1990, an upper digestive endoscopy combined with multiple gastric and duodenal biopsies was performed. Histologic examination of the bowel specimens revealed flattened villi, small intestinal mucosa laden with distended foamy macrophages in the lamina propria and intracellular periodic acid Schiff (PAS) positive granules (Figure 1A - 1B). Acid-fast bacilli were not identified in Ziehl-Neelsen stain. Electron microscopy promptly identified the causative agent and Whipple's disease was then confirmed (Figure 1C - 1D).

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Received 6 August 2003. Accepted 14 November 2003.

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Sulfamethoxazole-trimethoprim (SMZ-TMP) double dose (160 mg/800 mg) was started, with excellent response. Abdominal symptoms completely disappeared and he recovered weight. In 1992, treatment was interrupted.

Three years later, he presented with erectile dysfunction and lab tests showed hyperprolactinemia (87.6ng/ml) and low testosterone levels (13.7 pg/ml). Cranial computed tomography (CT) had no abnormal findings. Bromocriptine 2.5 mg/day was introduced leading to incomplete relief. In 1995, the patient developed progressive diplopia, gait disturbance, sensitive complaints and intense retro-ocular pain. Neurological examination showed an axial and left-sided cerebellar ataxia, accompanied by slow voluntary vertical saccades with diminished abduction of the left eye. Tactile and painful sensation were also impaired in the right side of the body, but no pyramidal or cognitive deficits were found. Cerebrospinal fluid (CSF) showed pleocytosis with lymphocyte predominance (55cells/mm³) and 2 PAS-positive cells. Serum folate and vitamin B12, thyroid function tests, anti-nuclear antibody titers, Venereal Disease Research Laboratory (VDRL) and human immunodeficiency virus (HIV) tests were all negative. Seven days after this first evaluation, lethargy and drowsiness developed. Another lumbar puncture was performed and CSF analysis revealed 2986 cells/mm³ (84% neutrophils), with increase in protein

concentration (215 mg/dl) and slight decrease in glucose concentration. Gram's stain, bacterial counterimmunoelectrophoresis and cultures were all negative. Ceftriaxone 1g b.i.d. was given for 14 days and there was marked improvement in the level of consciousness. Four weeks later, CSF analysis was normal and magnetic resonance imaging (MRI) findings revealed bilateral ovoid images in the lentiform nuclei, with neighboring T1 hyperintense and FLAIR hypointense lesions, without contrast enhancement (Figure 2A - 2B). The patient was then discharged taking again SMZ-TMP.

Over the next few months, ophthalmoparesis worsened, resulting in complete loss of voluntary vertical eye movements associated to medial deviation of the left ocular globe (left abducent nerve palsy). Vergence nystagmoid jerks of both eyes, which were synchronous with a soft chin tremor, soon developed, consistent with oculomasticatory myorhythmia (OMM). Additionally, primitive reflexes (such as snout, sucking, and palmomental) began to be noticed. There were no changes in clinical or neurological features until 2001, when depressive and amnesic complaints appeared.

At present (March 2003), besides cerebellar ataxia, he has signs of polyneuropathy (abolished Achillean reflexes and decreased vibratory sensation in the feet). Neuropsychological and neuropsychiatric assessment using CAMCOG/CAMDEX batteries reveals slight depres-

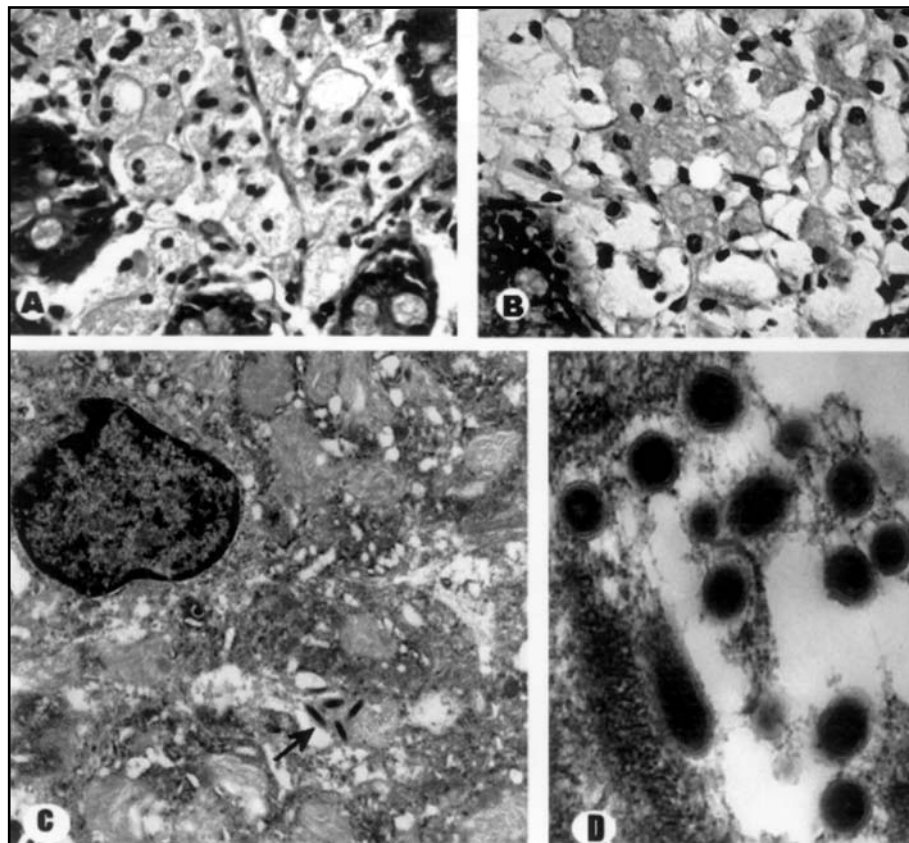


Fig 1. A - Small intestinal mucosa showing numerous macrophages with clear foamy cytoplasm in the lamina propria (HE, x 400). B - Some macrophages have slightly PAS positive cytoplasm (PAS, x 400). C - Electron micrograph showing a macrophage. The nucleus is in the upper left corner. The cytoplasm contains amorphous material and a small cluster of bacilli (arrow) (x 3600). D - Detail of bacilli in the cytoplasm of another cell. The bacilli appear homogeneously electron dense with double layered external wall (x 20000).

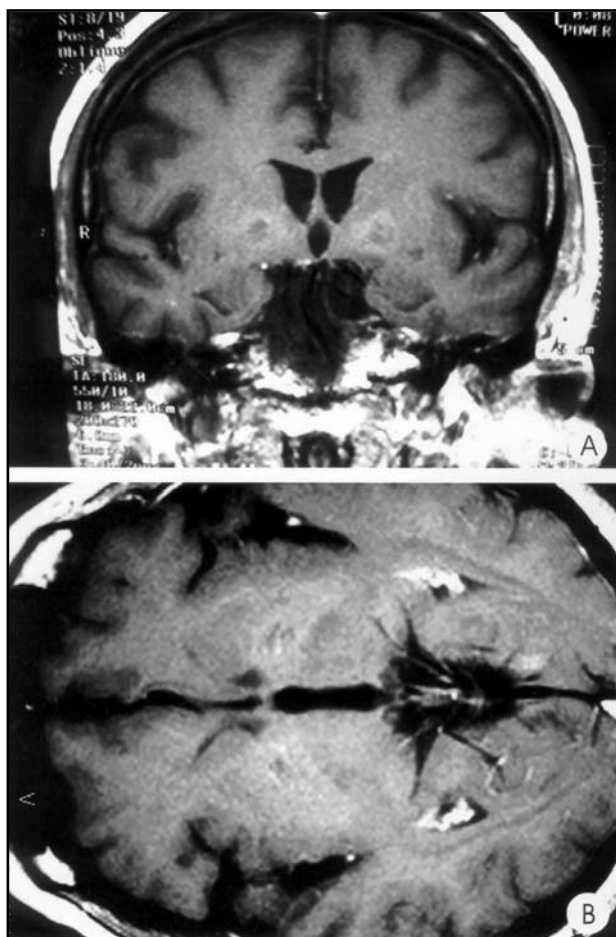


Fig 2. T1-weighted MRI showing bilateral ovoid lesions in the lentiform nuclei, with slightly hypointense center and surrounding hyperintensity. A) coronal view. B) axial view.

sive symptoms and mild dementia, with poor recall of 6 figures and 5 other items after a few minutes, impairment of constructional praxis and arithmetic calculation, but preserved time/place orientation and basic language skills (except dysarthria and rare word finding difficulties, without anomia). Single-photon emission computed tomography of the brain (^{99m}Tc ECD SPECT) shows diffuse and heterogeneous cortical hypoperfusion. The patient now takes SMZ-TMP, bromocriptine and fluoxetine on a regular basis. He keeps walking unassisted, without major functional limitations, and his cognitive deficits have not significantly progressed.

DISCUSSION

WD usually affects caucasian middle-aged individuals (mean age at diagnosis around 50 years) and is about 8 times more frequent in men. Recent epidemiological studies, including several familial cases, point to an apparent genetic conditioned susceptibility related to some HLA loci². This last finding strongly suggests that a host factor (defective T-helper cells of type 1 immunity) plays a key role in pathogenic events. Systemic manifestations are generally the presenting features of WD. Abdominal complaints, recurrent arthropathy and longstanding fever are

particularly common and precede diagnosis for a few years. However, any organ can be involved and there are reports of myocarditis/endocarditis^{5,6}, polyserositis², hepatosplenomegaly² and uveitis⁷. According to Louis et al.⁸, around 80% of CNS WD patients have systemic signs or symptoms at diagnosis. Therefore, in the appropriate clinical setting, considering WD in a patient with neurological deficits can be important.

CNS involvement was first described in 1958⁹ and much knowledge has emerged since then. Classical neuropathological features include generalized cerebral atrophy and diffusely scattered small chalky nodules in cortical and subependymal gray matter. In fact, these nodules are true granulomas that contain PAS-positive foamy macrophages and reactive astrocytes. Areas of intense demyelination (resembling multiple sclerosis) and microinfarcts are also sometimes identified in tissue specimens¹⁰.

Our patient first presented neurological manifestations two years after SMZ-TMP withdrawal. Such relapses of WD were frequently reported when initial antibiotic treatment had not been adequate and frequently included cerebral manifestations. Short-term use of SMZ-TMP or tetracycline (which does not cross the blood-brain barrier) were particularly related to CNS relapses^{11,12} and a worse clinical course. Feldman et al.¹³ reported a patient disclosing acute meningoencephalitis during a relapse of the disease whose abnormalities closely recalled our own patient.

There are still conflicting data related to the real prevalence of neurological signs and symptoms in WD. Recent review articles^{3,8} suggest that almost half of WD patients have indeed evidence of CNS dysfunction. These manifestations are quite diverse and traditionally include OMM, cognitive changes, voluntary gaze abnormalities, pyramidal signs, sensory deficits, hypothalamic manifestations, cranial nerve abnormalities, ataxia and seizures. Besides such clinical variability, some patterns of presentation should clearly point to the diagnosis. One example is the classic triad of dementia, supranuclear ophthalmoparesis and myoclonus, which is observed in roughly 10% of cases. In this regard, OMM has not been described in any other neurological disturbance to date and therefore could be considered pathognomonic of CNS WD. It occurs in 20% of cases and consists in the synchronous coupling of rhythmic contractions of masticatory muscles and the pendular vergence oscillations of both eyes at a slow rate (1-2Hz). This unique sign of WD seems to be caused by brain stem lesioning and somewhat resembles segmental spinal myoclonus¹⁴.

Cognitive changes are perhaps the most common neurological abnormalities in WD (71% of cases) and generally show incomplete response to the treatment. They tend to progress insidiously and are usually accompanied by depression, personality and behavioral changes. Previous reports

identified disabling impairment in the domains of sustained attention, memory, executive function and constructional praxis¹⁵. At later stages, these deficits completely fulfill criteria for dementia (much like Alzheimer's disease) and steadily worsen prognosis.

Voluntary gaze abnormalities preferentially affect vertical movements of the eyes and are noticed in half of the patients. There is usually progressive slowing of upward saccades, soon followed by downward saccades. Some affected individuals become virtually unable to look up or down at last and may receive a diagnosis of progressive supranuclear palsy (PSP). Isolated horizontal supranuclear gaze palsy is extremely uncommon, but combined impairment in both directions (horizontal and vertical) is frequently seen⁸. It is also interesting that all cases presenting OMM had vertical supranuclear palsy.

Internuclear ophthalmoplegia, pupillary abnormalities and ptosis have been described in isolated WD patients. Oculomotor (III), trochlear (IV) and abducens (VI) palsies are not usual either, but reported in at least 5% of affected individuals⁷. Together, cranial nerve abnormalities occur in 25% of cases.

Hypothalamic involvement has been clearly identified in previous papers¹⁶⁻¹⁸. Sleep/arousal disturbances, hyperphagia and polydipsia were reported in 31% of cases.

Similarly, endocrine deficits related to hypopituitarism were recognized in the setting of CNS WD¹⁹. These patients presented with signs of hypothyroidism, complaints of erectile dysfunction (just like our case) or galactorrhoea and had good response to antimicrobial and hormonal replacement therapy.

Pyramidal and sensation deficits are other signs of CNS derangement recorded in WD, just as myoclonus and seizures, which are noticed in almost one fourth of patients. Additionally, gait and stance instability related to cerebellar damage occur in 20% of patients, being a major source of functional impairment⁸. A few cases presenting with rapidly evolving cranial hypertension were reported, most of them caused by tumor-like lesions or acute hydrocephalus (Sylvius aqueduct stenosis)^{3,11}. Various forms of peripheral neuropathy have been observed as in other chronic inflammatory bowel diseases, probably associated to malabsorptive nutritional deficiencies²⁰. Conversely, spinal cord^{3,21} and muscle³ involvement are exceedingly uncommon.

Once suspected, WD has been classically confirmed by intestinal biopsy and histopathological analysis (PAS staining and EM) in at least 80% of affected individuals. Particularly in CNS WD, it is accurate in 70% of cases even if there are no abdominal complaints. Hence, patients with neurological deficits compatible with WD should initially have an upper digestive endoscopy and duodenal biopsy. Recently, polymerase chain-reaction (PCR) has been used to confirm the diagnosis

of WD². This is emerging as a promising technique with high sensibility and specificity²². Positive results of PCR assays against *Tropheryma whipplei* have been obtained from several tissues, including brain and CSF²³. Therefore, PCR will probably become an interesting tool for WD diagnosis (particularly for CNS restricted disease) and long-term follow up. Microbial cultures and serology are of little diagnostic help yet.

Neuroimaging and CSF analysis are usually undertaken and can be diagnostically useful. Brain MRI findings in WD are largely non-specific²⁴. Lesions tend to affect in decreasing order of frequency, cerebral frontal cortex, basal ganglia, periventricular white matter, hypothalamus, temporal and parietal cortex³. Similarly, CSF non-specific abnormalities have been identified in at least half of patients⁸. Most had slight CSF protein elevation, lymphocyte pleocytosis and PAS-positive cells. Nevertheless, some authors report acute meningitic presentations with marked pleocytosis with polymorphonuclear predominance^{25,26}.

Diagnostic guidelines based on available data were ultimately proposed by Louis et al.⁸. These authors considered the diagnosis of CNS WD definite in patients having at least one of the following criteria: 1. OMM; 2. positive tissue biopsy (PAS-positive cells); 3. positive PCR analysis. Additionally, if histological or PCR analysis were not performed on CNS tissue, then the patient must also demonstrate compatible neurological signs (supranuclear vertical gaze palsy, rhythmic myoclonus, dementia or hypothalamic manifestations). Our patient clearly matches these criteria, having laboratory and clinical evidence of CNS WD.

In the past, several antibiotic regimens were used for WD without convincing results. The proper choice of an effective drug is now recognized as an essential part of the treatment, lessening the risks for future CNS relapses^{27,28}. Oral SMZ-TMP (160mg/800mg bid) is the currently recommended long-term therapy and should be prescribed for at least one year^{2,29}. In addition, a 2-week course of parenteral therapy consisting of ceftriaxone 2g/day is strongly suggested in severely ill patients and must precede maintenance therapeutics. Alternative approaches using penicillin plus streptomycin or minocycline have been used on an individual basis and can be applied in cases of sulfonamide intolerance.

These directions led to a lower rate of clinical relapses and a much better long-term outcome. SMZ-TMP was particularly effective for CNS WD patients, improving or at least stabilizing their course³. Nevertheless, the precise duration of antimicrobial treatment and the best follow-up approach must still be determined. In some resistant cases, therapy is still a challenge but recent reports² on the use of supportive gamma interferon seem very promising.

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