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# HYPERSOMNIA IN WHIPPLE DISEASE

## Case report

*Luís F. Maia[1], Mónica Marta[1], Vitor Lopes[2], Nelson Rocha[2], Carlos Lopes[3], Antônio Martins-da-Silva[1], Luís Monteiro[1]*

ABSTRACT - Whipple disease (WD) is a rare systemic infection caused by *Tropheryma whippelii.* Neurological involvement has been recognised in 40% of patients, either as initial manifestations or during the course of the disease. We report on a 45 years-old man with WD with initial, persistent and irresistible episodes of daytime somnolence. The patient was HLA-DQB1*0602 positive (genetic marker for narcolepsy). WD diagnosis was suspected on clinical and MRI basis and confirmed by histological and immunohistochemical study of duodenal biopsy. Forty months later all clinical features improved, narcoleptic-like episodes disappeared and cerebral MRI and CSF normalised. Longitudinal neurophysiological studies revealed persistent sleep pattern abnormalities with sleep fragmentation, paucity of slow wave and of REM sleep. The disruption of the hypocretin circuitry in the hypothalamic - diencephalic region triggered by the infection was the probable cause of the hypersomnia and narcopleptic symptoms. WD should be added to the list of causes of secondary hypersomnia.

KEY WORDS: Whipple disease, hypersomnia, multiple sleep latency test, HLA (DQB1*0602).

**Hipersónia na doença de Whipple: relato de caso**

RESUMO - A doença de Whipple (DW) é infecção sistémica rara causada pelo *Tropheryma whippelii.* Cerca de 40% dos doentes apresentam envolvimento neurológico, seja como manifestação inicial da doença, seja durante o seu curso. Apresentamos o caso de um homem de 45 anos com doença de DW com episódios iniciais, persistentes e irresistíveis de sonolência durante a actividade diurna. O doente era positivo para o HLA-DQB1*0602 (marcador genético de narcolepsia). A suspeita do diagnóstico de DW foi levantada com base na clínica e RM e confirmada por estudo imunocitoquímico do material de biópsia jejunal. Quarenta meses mais tarde, todas as manifestações clínicas melhoraram, os episódios narcolépticos desapareceram, e a RM e o LCR normalizaram. Os estudos neurofisiológicos seriados do sono revelaram alterações persistentes caracterizadas por fragmentação do sono, escassez de ondas lentas e sono REM. A perturbação do circuito da hipocretina na região hipotálamo-diencefálica, causada pela infecção, foi a causa provável da hipersónia num doente geneticamente susceptível. A DW deve ser incluída nas causas de hipersónia secundária.

PALAVRAS-CHAVE: doença de Whipple, hipersónia, teste de latências múltiplas, HLA (DQB1*0602).

When George H Whipple first described in 1907 the autopsy findings of a case of "intestinal lipodystrophy" no neurological manifestations were reported and pathology of central nervous system (CNS) was not described. Whipple disease (WD) was born. It is now believed that the CNS is the major extra-intestinal site of involvement[1,2]. Data in the literature report a variable frequency of neurological symptomatology of 5-40% with only 5% with exclusive CNS involvement[1-4]. WD is caused by *Tropheryma whippelii* (TW) and it is generally accepted that both the presence of the bacillus and the host response are responsible for the clinical manifestations of WD[1,2]. Classic symptoms and signs of neurological involvement are: vertical ophthalmoplegia, segmental myorhythmia, myoclonus, dementia and hypothalamic manifestations such as hyperphagia and changes in libido[3,4]. Sleep disturbances mimicking narcolepsy are exceptional[5].

We report the clinical, biochemical, brain imag-

[1]Department of Neurological Disorders and Senses, Hospital Geral de Santo António, Porto, Portugal; [2]Department of Medicine, Hospital Geral de Santo António, Porto, Portugal; [3]Hospital de Barcelos, Barcelos, Portugal.

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*Dr. Luís Monteiro - Department of Neurological Disorders and Senses - Hospital Geral Santo António - Largo Prof. Abel Salazar - 4099-001 Porto - Portugal. E-mail: luismonteiro.neuro@hgsa.min-saude.pt*

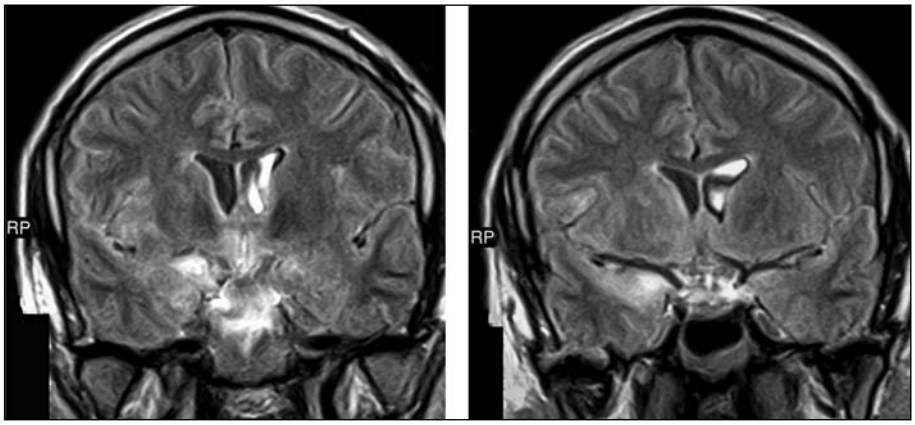


*Fig 1. MRI images after gadolinium contrast injection: patchy contrast enhanced lesions in the insula and hippocampus in the right and in the hypothalamic-diencephalic region.*

ing, HLA genetic characterization, polysomnographic findings and outcome of a patient with sudden episodes of hypersomnia, in whom WD was diagnosed by duodenal biopsy. To the best of our knowledge, this the first description of a case in which frequent episodes of irresistible daytime somnolence (resembling narcolepsy) are the initial, predominant, and the most disturbing presenting feature of cerebral WD.

## CASE

A 45 year-old man, stone-mason, previously healthy, was admitted with a 6 months history of frequent episodes of sudden daytime sleepiness occurring while working, eating meals or even during showering. It would be difficult to wake him up and the irresistible urge to sleep was becoming increasingly frequent. Night time sleep was restless, with periods of sleepwalking, witnessed in several occasions by relatives. After daytime sleep periods a frontal headache was reported, lasting for about two hours. In the course of the disease, the headache became generalized and permanent. During this period the patient ate more than usual and gained 10 kg, exhibiting decreased libido and psychomotor slowness. He also reported in the past, on direct inquiry, short periods of polyarthralgias. Neither diarrhoea or other gastrointestinal symptoms were referred.

In the course of hospitalization the patient neurologic status was characterized by: 1- hypothalamic-diencephalic syndrome with frequent irresistible episodes of daytime somnolence, hyperphagia, decreased libido and mild persistent hyponatremia; 2- neuro-ophthalmologic syndrome with apraxia of lateral gaze and supranuclear ophthalmoparesis; 3- myoclonic syndrome with neck and right arm segmental myoclonus, perioral and left laterocervical myorhythmia; 4- frontal lobe syndrome with apathy, lack of initiative and psychomotor slowness. Other medical systems examination was normal.

Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (20 cells/μL; 77% lymphocytes, 10% monocytes, 13% polymorphonuclear leukocytes), normal glucose (0.60 g/L) and protein (0.27 g/L). His complete blood count, erythrocyte sedimentation rate, electrolytes, renal, hepatic and thyroid function, B12 vitamin and folic acid level and serum angiotensin conversion enzyme were normal. The serological tests for HIV 1 and 2, syphilis, borrelia, herpes I and II, Epstein Barr virus, cytomegalovirus, Mycoplasma and legionella were negative for acute infection.

Brain MR imaging showed hyperintense signal on T2 weighted images on the caudate head, frontal operculum, insula, hipocampus, right amygdalo-hipocampal transition and hypothalamo-diencephalic region. All these areas enhanced after gadolinium injection (Fig 1).

Based on the presence of supranuclear ophthalmoplegia, segmental myoclonus and sub-cortical dementia cerebral, WD was suspected, in spite of the absence of gastrointestinal symptoms. Histology of duodenal tissue showed a lymphoplasmacytic inflammatory infiltrate with PAS positive staining histiocytes on optic microscopy and the identification of the characteristic rod-shape intracellular organism by electron microscopy (Fig 2). The same tissue tested positive for anti-TWi antibodies by immuno-histochemical

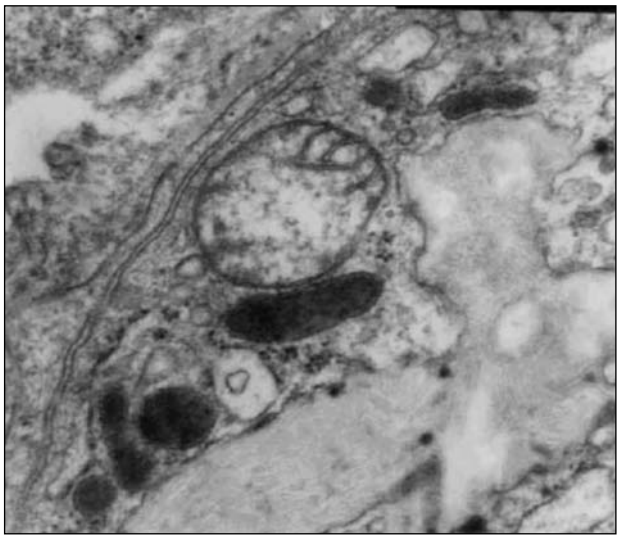

*Fig 2. Electron microscopy: Intra-cellular rod-shaped T. Whippelii.*

*Table. Main characteristics of all sleep (night and day recordings). Sleep time, sleep latency and total sleep time are in minutes.*

| Recording type (Record #) | Sleep latency | Total sleep time | Sleep efficiency | Sleep structure | REM sleep and REM latency | Respiratory dysfunction | Notes |
|---|---|---|---|---|---|---|---|
| Day recording (R 1) | nsr | 0 | 0 | nsr | nsr | No | No sleep recorded |
| MSLT (R 2) | 13' Nap 3 | na | na | na | No REM | No | Continuous sleep SII on Nap 3 – Nap 4 |
| Night sleep (R 3) | 344 | 300 | 46% | SII and occasionally SIII | No REM | No | |
| MSLT (R4), affter R3 | nsr | 0 | 0 | nsr | nsr | No | No sleep recorded |
| Night sleep (R 5) | nsr | 0 | 0 | Short periods SI- SII | No REM | No | Night Insomnia (short epochs of SI-SII) |
| Night sleep (R 6) | 161 | 328 | 50.2% | SII-SIII, occasionally SIV | Few REM | Yes: Sleep apnoea (RDI : Mean 16/H) | Total 100 apnoeas (mean 02 Sat =95%) |
| MSLT (R 7) after R6 | nsr | 0 | 0 | nsr | nsr | No | No sleep recorded |

nsr, no sleep recorded; na, not aplicable.

analysis. Polymerase chain reaction (PCR) CSF analysis was negative. All these data confirmed the clinical diagnosis of WD. HLA studies reveal the presence of the DBQ1*0602 haplotype. Hypocretin studies were not available. Antibiotic treatment started with ceftriaxone IV and streptomycin IM during 4 weeks followed by oral cotrimoxazole the following 18 months

During hospitalization and follow-up, sleep was studied seven times (summary of the results are on Table). Initially a daytime registration was unsuccessful because the patient did not fall asleep. Only myoclonic jerks were recorded (Record 1, or R1, on Table). Three MSLT were performed, two out of them followed the APSS Committee Guidelines[6]. On first MSLT (R2) an irresistible sleep episode occurred on Nap 3 (patient fall asleep on Sleep SII and remains asleep until the end of MLST; no REM period was present). Four weeks after started treatment a nocturnal recording was performed preceded by a routine EEG at waking period. On night sleep recording (R3) a marked disruption of sleep structure was evident: sleep SII predominant and loss of SWS with limited efficiency (46%). No REM sleep was present. The MSLT on the following morning/day (R4) did not record sleep. Thirty months later myoclonus resolved and very significant regression of the dementia, ocular apraxia and vertical ophthalmoparesis. Although attenuated, rare episodes of hypersomnia still persisted. At that time CSF and brain MRI studies were normal. In spite of the clinical and laboratorial improvement, night sleep recording (R5) showed almost total insomnia with only short periods of SI-SII. Studies performed at 40 months after disease beginning (R6 and 7) showed initial insomnia (Sleep Latency 161 minutes) partial improvement of sleep structure with very short SIV, better sleep efficiency (50%) and incipient REM sleep. A new sleep feature was the recording of more than 100 obstructive sleep apnoeas, with RDI surpassing 16/hour without significant decrease on O2 saturation. The MSLT did not record sleep. The initial prominent sleep features were the extended sleep latency, the paucity of slow wave sleep and the sleep fragmentation and absence of significant REM. Sleep improvement was noted in the last and more recent nocturnal sleep study, in which obstructive sleep apnoeas were recorded.

The patient give informed consent for publication of the case.

## DISCUSSION

Whipple disease is a rare systemic infectious disorder with prominent but not invariable gastrointestinal involvement. In the present study the patient with cerebral WD had a clinical picture of myoclonus, segmental myorhythmias, supranuclear ophthalmoparesis, and sudden episodes of hypersomnia[1,3,4]. This CNS multifocal involvement translated into signs and symptoms suggesting WD prompted us to carry out a duodenal biopsy which confirmed the clinical diagnosis. The peculiarity of this case is the diurnal irresistible episodes of sleep resembling narcolepsy (but without REM sleep episodes recorded in MSLT), as the prominent and initial clinical feature. This is, to our knowledge, for the first time described in detail by longitudinal PSG records. In previous descriptions, sleep disturbances in WD patients are just mentioned[5,7,8]. A case of persistent and prolonged insomnia, however, was recently studied in detail[9].

In our patient the episodes of irresistible sleep

were confirmed by witness (including video by authors) and on MSLT, although without recording of REM episodes, pointed to the diagnosis of "possible" narcolepsy[10]. However, REM episodes as seen in classical forms could be absent in secondary narcolepsy[11]. Secondary narcolepsy is rare but is known to occur in cerebral sarcoidosis, pituitary lesions, craniopharyngiomas, strokes, multiple sclerosis, HIV encephalopathy, arteriovenous malformations and tumours involving the posterior hypothalamus[11,12]. An exception is the anti-Ma2 associated encephalitis where narcolepsy is frequent[13]. The fact that our patient is HLA DQB1*0602-positive, a strong genetic marker for narcolepy, suggests that, in an appropriate setting, promoting the disruption of the hypocretin circuitry an unnoticed subclinical disease may be revealed[10,14]. The clinical picture improved significantly after antibiotic treatment. However, the last PSG (40 months later) showed a disturbed sleep structure with sleep apnoea.

It is generally accepted that the hypothalamus is involved in the control of the circadian rhythm, via the suprachiasmatic nucleus and their connections including hypothalamic and diencephalic areas is relevant to the wake-sleep cycle generation[15,16]. In our patient the mechanism through which these sleep disturbances occurred is speculative. However the association of an genetic marker for narcolepsy (HLA-DBQ1*0602 haplotype) and a disease involving the hypothalamic diencephalic region may have triggered the disruption of the neurobiological control of sleep-wakefulness in a highly susceptible narcoleptic type patient. After a follow-up period of more than three years, the therapy induced a progressive and sustained clinical improvement with disappearance of all cerebral lesions seen on the first MRI. A satisfactory evolution like that observed with our patient is rare in CNS involvement of WD[3,4].

In conclusion, clinical suspicion, confirmed by duodenal biopsy or PCR studies in the CSF, is the hallmark of the diagnosis of cerebral WD, which should be considered on the investigation of sleep disturbances, particularly when associated to daytime somnolence and narcolepsy-like attacks.

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