Frontal lobe syndrome with psychotic symptoms secondary to a giant meningioma in a 38 year old man

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Dear Editor,

The estimated prevalence of brain tumors is 27.5 per 100,000 of the population; 35.8% of primary brain tumors are meningioma, and 54.3% of non-malignant primary brain tumors originate in the meninges[1]. The etiology of meningioma has remained unclear for two main reasons: 1) their evolution time, which usually varies from 20 to 30 years; 2) they are often incidentally discovered, and autopsy studies indicate a subclinical prevalence of 2.8% of the population[2]. The 88% of brain tumors cases and psychiatric symptoms are located in the frontal region[3]. This article exposes the case of a young adult with psychotic symptoms secondary to a meningioma, attended to by psychiatric emergency services.

Case report

The subject is a 38 year-old man. Nine months prior to receiving psychiatric care, he began to present the following symptoms: unquantified weight loss, irritability, neglect of hygiene and cleanliness, and apathy. His family attributed this to the consumption of alcohol and cocaine, the latter initially being unknown, and which led him to be admitted into the addiction treatment center for three months. During that time, he experienced a weight loss of about 30 kg, episodes of loss of vesicle control, difficulties walking, failures in spatial and time orientation, passivity, poor judgment and episodes of physical and/or verbal aggression, all this without receiving specialized medical attention. These symptoms worsened one month before the individual entered the psychiatric hospital. Additionally, he presented a deluded attitude, muttering, outbursts aggressive, unstructured delusions and commisions of serious errors in judgment (he threatened his wife and attempted to throw his daughter out of the window). For these latter incidents, he was brought to the psychiatric emergency room.

Family background: No neuropsychiatric history. Personal background: Product of the 4/5, born without any apparent perinatal complications; psychobiological development apparently normal. No reported allergies, surgeries, transfusions or brain trauma. Consumption of alcohol and tobacco (smoking) since the age of 13, unknown consumption pattern but has stopped consuming alcohol seven months ago and continues to smoke one pack of cigarettes per day. Cocaine use is reported without any specification of quantity or frequency. Psychosexual history: multiple sexual partners, denies having contracted any sexually transmitted diseases. Personality Traits: manipulative, lying, poor social adaptation, dishonesty and irritability. Professional experience: Multiple underemployment, and has been unemployed for the last year. Educational experience: lack of discipline provoked low performance at school due to untreated behavior alteration throughout childhood; lack of interest led him to abandon his studies before finishing secondary school.

Mental Examination: The patient had an uncooperative, expressionless attitude and did not make eye contact with the interviewer. His attention and understanding diminished, and he did not follow basic orders. He was oriented to person, but disoriented with respect to time, place and circumstance. His mental functions (calculation, abstraction, memory) were not evaluable. His language was of low volume and bradiplalia. Thought: do not follow guidelines, laconic and monosyllabic answers. Delusions not integrated and not hallucinate. His judgement was suspended, and his affect is indifferent.

Physical examination: Vital signs: BP 120/70, CF 70, RF 18, Temperature: 36.5. Normal skull, isochoric pupils. Oral mucosa regularly hydrated. Neck: unaltered. Chest: no data or sign of respiratory distress; well ventilated lung; rhythmic heart sounds, adequate intensity and frequency. Abdomen: soft, depressible but not painful. Thoracic members: decreased muscle strength in four limbs, predominantly left hyperreflexia. Inability to follow complex orders showed deteriorated mental functions. Disoriented in time and space. Cranial nerves: Normal. Overall decreased muscle strength: thoracic limbs 4/5 and pelvic limbs 3/5. Reflections ++ in pelvic limbs and + in thoracic limbs; tone and trofismo diminished. Sensitivity for light touch and pain is preserved. Impress loss of proprioception in both pelvic limbs. Cerebellum unaltered although difficult to explore; ineptitude to function due to weakness. Not meningeal or atavistic signs.

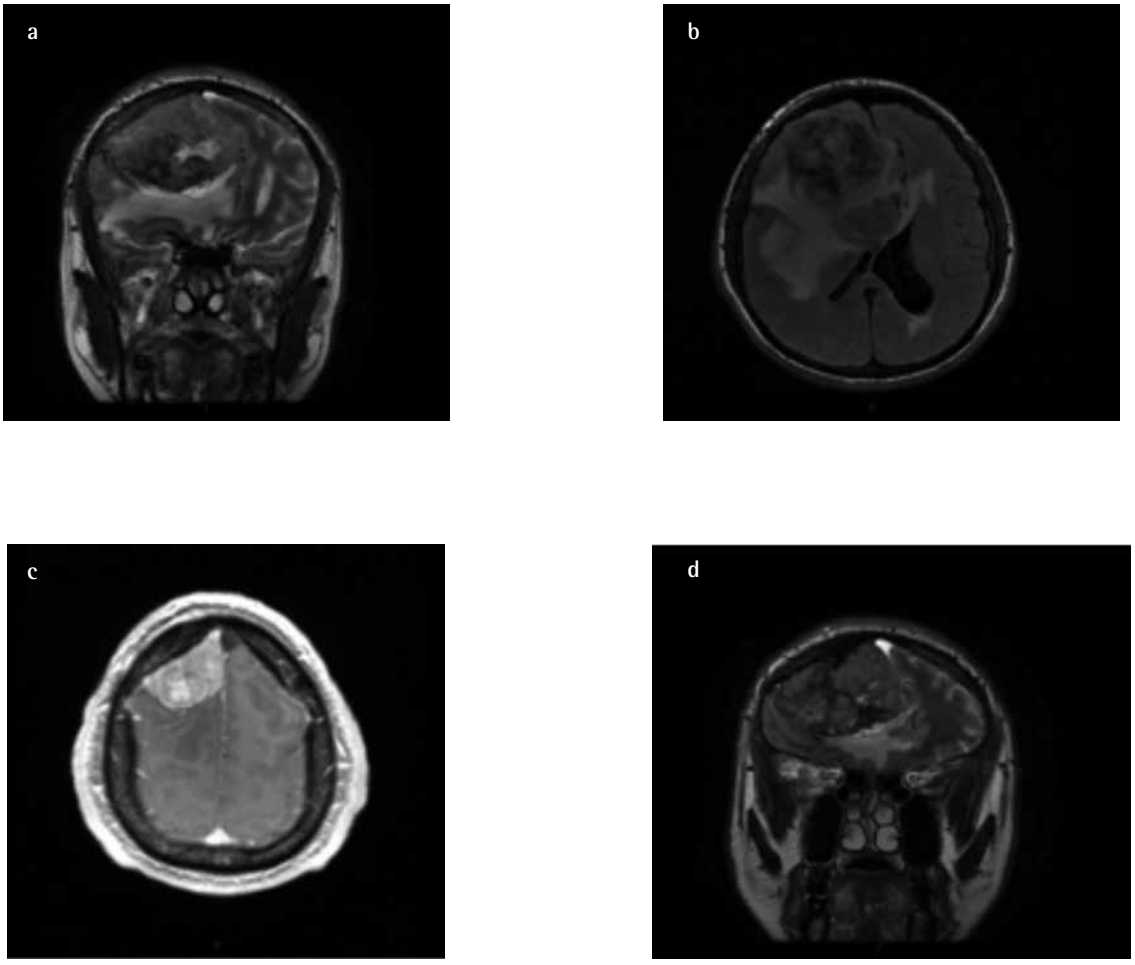
Laboratory studies: Blood Count: normal. Blood chemistry: normal. Liver function test: Indirect Bilirubin 1.16 mg/dl and bilirubin Total 1.34 mg/dl. Thyroid Function: normal. Lipids: normal. HIV: negative. Serum electrolytes: normal. Image study: show MRI brain coronal and axial slices, in sequences (T1 and T2 flair). Extraxial injury, isointerna to gray matter, located in right fronto-parietal region, which affects compression of the ipsilateral ventricular system, displacement of the middle line, and compression subfaccial hernia

contralateral lateral ventricle was observed. The perilesional edema affects the right temporal lobe (Figure 1). The patient was sent to another medical unit for surgical treatment; the histopathological study reported a meningioma.

Discussion

Psychiatric symptoms secondary to medical causes are not uncommon in psychiatric emergency rooms. The present case showed psychotic symptoms, a history of substance use, risk factors for sexually transmitted diseases, and antisocial personality traits. Clinical observation and clinical information provided by the family led to the diagnosis of a frontal lobe syndrome, which was confirmed by an imaging study.

The extension of the patient's meningioma involved the right fronto-parietal region, damaging the medial lateral orbitofrontal circuit, a region anterior to the cingulum and the dorsolateral prefrontal cortex, which explains the symptomatology that was, described[4]. Table 1 shows the clinical presentation and anatomical correlation. The compression and perilesional edema of the right temporal lobe, an area associated with face recognition and familiarity (a capacity was



In a), c) extraxial injury, isointerna to gray matter, located in right fronto-parietal region, which affects compression of the ipsilateral ventricular system, displacement of the middle line, and compression subfaccial hernia contralateral lateral ventricle. The perilesional edema affects the right temporal lobe show in b), d).

Figure 1 | *MRI brain coronal and axial slices Meningioma*

Table 1 Clinical anatomical correlation

Symptomatic manifestations in the patient.	Time evolution prior to the patient's admission	Anatomical region engaged (Function)
Disorders in recognition or sense of familiarity of persons (attempted to throw his daughter out of the window). Misidentification delusions.	1 month	Temporo-parietal right (Recognition of persons)
Diminished judgment, self-care. Perseveration.	9 months	Dorsal lateral prefrontal (Cognition)
Anhedonia, depression, dysphoria. Diminished social insight, irritability.	9-6 months	Lateral orbito-frontal (Social behavior)
Apathy diminished spontaneous prosody. Explosive aggressive. Urinary incontinence.	6-3 months	Mesial frontal (Motivation)

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lost in our patient) maybe led to delusions and aggressive behavior directed toward his daughter, similar to Capgras syndrome.

This type of presentation is unusual for a patient of this age: the incidence in the present patient's age range of 35-44 years of age is 1 per 100,000 of the population, versus 20 per 100,000 of the population between 75 and 84 years old (the average age at diagnosis is 65 years). In all age ranges, the prevalence of primary brain tumors is higher in females, particularly meningiomas and pituitary tumors, as well as subclinical prevalence of 2.8% according to autopsy studies. Incidence of brain tumors in females is twice than males 8.36 and 3.61 respectively. Males have a higher prevalence of glioma[1].

The incidence of meningiomas is predominant in females, and is attributed to hormonal factors, as changes have been reported associated with estrogen and progestogen cycles. Another factor associated with increased risk for brain tumors is having a Body Mass Index (BMI) above the norm[5]. Recent meta-analyses have reported a significant association between smoking and increased risk of meningiomas in men[6].

In the present case, one possible risk factor that was detected is chronic smoking; however, there is no conclusive evidence that this or any other factors are associated with some type1 of primary brain tumor. An important corollary should be emphasized: during any clinical evaluation in psychiatric emergencies, the possibility that the symptoms are due to structural medical causes should always be considered.

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CONFLICT OF INTEREST

None to declare

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A Study of Clozapine-Induced Sedation

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Dear Editor,

Clozapine is the most effective antipsychotic[1] but its use is limited to drug-resistant cases due to the potential life-threatening side effects as agranulocytosis and neutropenia, which requires monthly haematological monitoring. The need for monthly monitoring also provides an opportunity to understand other clozapine related complications, such as sedation. Clozapine is ranked as the most sedative antipsychotic[2] although literature studying its impact in activities of daily life is scarce.

The Cambridge walk-in clinic opens each Wednesday from 9am to 3pm to accommodate 197 patients diagnosed with schizophrenia and related disorders (F20-F25 ICD-10). Patients are invited to a specific day but not specific time to get the blood monitoring. We hypothesized that measuring the arrival time could provide a proxy measure of the impact of sedation in daily life an aspect related with functionality. The exact arrival time to the clinic was recorded in two consecutive time points, day-1 (d1) and day-2 (d2) separated by 28 days. Clinical information was then obtained using the Clinical Record Interactive Search (CRIS)[3] of the Cambridgeshire and Peterborough NHS Foundation Trust (CPFT). We also obtained other variables that were used for the bivariate correlations and multiple regression models, including age, gender, clozapine total and night dose and other prescribed drugs (yes/no).

The final sample included 184 subjects [75% men, mean age 43.83 years (SD=10.68)] in which we recorded the arrival time at d1. Arrival time on d2 was available on 176 cases (figure 1). The majority of patients arrived before midday (d1=69%; d2=64.8%) with peak between 9 and 10am (d1=25%; d2=24%). Bivariate associations revealed that the arrival time did not correlate with the age, the total clozapine dose or night dose (r=-.131 p=.072; r=.009 p=.91 and r=.013 p=.86, respectively). On average, women arrived 32 minutes (standard deviation=14) earlier than men (t=-2.29, p=.023). No correlation was found between the arrival time and the use of other psychotropic. Multivariate linear regression analysis using arrival time as independent variable and gender, age, clozapine dose, percentage night dose and concomitant use of sedatives (yes/no) was performed and only gender was significant (p=.032). Interestingly, the correlation between d1 and d2 was highly significant (r=.626, p<.001).

Contrary to our prediction, patients choose to turn up during the earlier hours of the clinic, suggesting that the impact of sedation in functioning during first hours in the morning on the majority of them could be less than expected. Other factors such as working commitments or family and patient worries about risk of agranulocitosis could influence in their behavior, although this is unlikely to affect the results, as the vast majority of patients are unemployed and they have been on clozapine medication for years.

Clozapine factors, such as total and night dose, had little influence on the arrival time and indeed other authors have concluded that clozapine dose and plasma levels had poor correlation with side effects[4]. A potential explanation of these apparently contra intuitive result could be that persistent sedation and sedation auto-perception might be

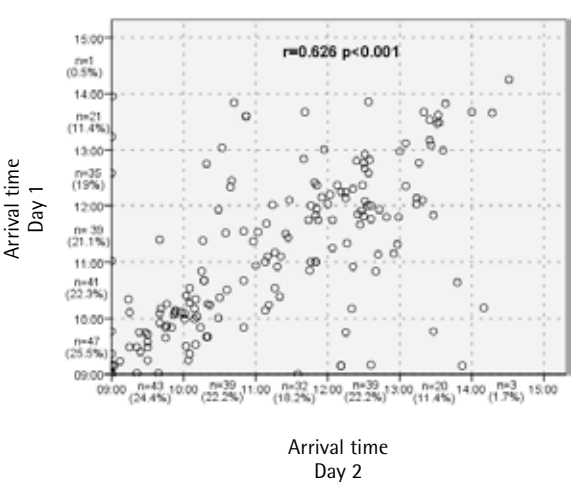

Figure 1 — *Plot of Day 1 and Day 2 arrival time and its correlation. Axis Y and X also include the number of patients and percentage arriving in each range of hour*

influenced by lack of daily routine and daily schedule. By definition, most of clozapine patients are diagnosed with treatment resistant schizophrenia, with greater prevalence of unemployment, reduced social network and negative and cognitive symptoms and therefore poor daily structure and greater functional impairment. The blood test appointment day would represent the exception day when patients would commit themselves to planning before the awaking time, how to travel to the clinic..., and therefore decreasing the impact of sedation. In this way, development of rehabilitation programs which promote the own resources of planning and timing management are key points to improve the patient functioning and autonomy ant to facilitate psychosocial integration.

An unexpected finding in our results is that service users are consistent and arrive at a similar time every blood-testing day. There is not a clear explanation for this, as the current study did not address this question specifically. An intriguing hypothesis is whether this might be part of the clozapine-induced phenomena. Clozapine induced obsessiveness is a relatively newly described phenomena that has grasp interest in literature in recent years[5]. Obsessiveness is characterized by rigid and perseverative behaviour rather than guided by outcome and is more frequently observed in clozapine treated patients (up to 30%)[6] than in other schizophrenia subgroup. Our finding might be taken as an example of repetitive behavior, although specific studies should be designed in order to confirm this hypothesis.

Some limitations must be considered. First of all, our sample size was relatively small so the generalization of these findings needs to be tested in larger populations, although it might be difficult because walk-in clinics are rare. Secondly, we used the arrival time as a proxy measure of the impact of sedation in daily life, but the blood test appointment only represent one day per month. Finally, we only studied two point times for each patient. However, the bivariate scatter plot applied to investigate the association between the arrival time in two target days was significant, so we assumed it could be extrapolated to other blood test days.

Measuring the arrival time to the walk-in clinic provides an objective measure of the impact of sedation in daily life, without observer or patient bias. In our study this impact has result lower than we expected. Studies analyzing objectively potential impact factors for dysfunctionality should be carried out. By this way, better therapeutic tools for improving the global functionality in schizophrenia could be developed.

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Letter to the editor

Whippleian dementia

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Dear Editor,

Whipple's disease (WD) is a rare, multi-systemic, chronic and relapsing infectious disease caused by Tropheryma Whipplei. In 1907, GH Whipple described the illness[1], whereas the infectious origin was not confirmed until 1961[2]. Even though Tropheryma Whipplei is a ubiquitous environmental bacterium[3], it rarely causes the clinical illness to its carriers[4], suggesting a genetic vulnerability to its development[5,6]. Family cases have been described, although familial aggregation has not been proved[7]. Neither its natural source has not been defined, considering the fecal-oral transmission the most probable rout[8,9]. There are several presentations linked to Tropheryma Whipplei. Classic WD includes diverse clinical manifestations, being the most common symptoms weight loss, gastrointestinal and joint manifestations[10]. Other manifestations involve multiple organs and body systems, including the lymphatic system, pulmonary and cardiovascular system and the central nervous system (CNS)[10]. Neurological involvement affects up to 10%-43% of patients[11-17]. Moreover, 5% of patients present with isolated neurologic involvement[15,18-25]. Neurological signs are non-specific, thus it can almost imitate any neurologic condition[15,17].

We report a case of a patient with unusual neuropsychiatric manifestations, who was initially diagnosed with different affective disorders, but finally diagnosed with WD after a torpid evolution.

Clinical Case

Mr. X, 63 years old, was admitted to hospital at the psychiatry unit as a result of frequent and almost daily medical assistance at the emergency service due to depressive and anxiety symptoms and unspecific somatic complaints. After the first admission, a diagnosis of depression was established being once again hospitalized two months later. Subsequently, he was admitted at the neurology service suffering from apathy, irritability, psychomotor restlessness, cognitive impairment, tremor and ataxia. During the hospitalizations a large list of diagnostic test were done (table 1) in order to rule out a medical condition. Except for non-specific findings at the cerebral magnetic resonance, all tests performed were normal at that time. The brain magnetic resonance (MR) images showed the presence of brain damage suggestive of chronic small vessel ischemia in different localizations (basal ganglia, protuberance and right cerebellar hemisphere). The clinical impression pointed toward a major depressive disorder in a man with an emerging cognitive impairment.

Given the lack of response to treatment, the therapeutic approach consisted in a combination of antidepressants (selective serotonin and noradrenaline reuptake inhibitors and adrenergic $\alpha 2$ and 5-HT_{2A} antagonists) with lithium salts. Three weeks after the last admission, he was again hospitalized because of an abrupt worsening of depressive symptoms with mood congruent psychotic symptoms, cognitive impairment and drastic weight loss. The patient did not show gastrointestinal symptoms, neither articular nor other somatic manifestations, and the physical exam showed no relevant findings. The neurological evaluation revealed spatial and temporal disorientation, hypoprosexia and slight cogwheel rigidity. The neuropsychological assessment offered an important impairment of executive functions, visuospatial abilities and memory.

The patient's atypical manifestations and clinical evolution led to the need of additional tests, with a multidisciplinary approach including a group of physicians of different specialties such us psychiatrists, neurologists and internists. Blood test included hormones, tumor and autoimmune markers, and showed high levels of inflammatory markers (PCR, ESR and homocysteine). Serology for viral hepatitis, Coxiella Burnetti, Influenza, Legionella, Mycoplasma, Clamydia and Clostridium were negative, as were serology tests for HIV and Syphilis tested in previous admissions (see table 1). Blood and urine cultures were also negative. The EEG showed a diffuse slowing brain activity, and the transcranial ECO-Doppler revealed no pathological findings. A second cerebral MRI didn´t show new findings.

Analysis of cerebrospinal fluid (CSF) revealed high levels of proteins, with normal glucose and without oligoclonal bands. Furthermore, common microbiological tests were also negative in CSF (Gram and direct vision, culture; PCR, VHS, varicella, enterovirus and TB). The only finding was a low level of β-Amyloid, with normal levels of TAU and fosfo-TAU proteins. In the face of ongoing lack of response to treatment and the atypical neuropsychiatric symptoms, the weight loss, and the persistence of high levels of inflammatory markers, after ruling out the most common potential

Table 1 Hospitalization characteristics

Hospitalization	Psychiatric symptoms	Neurologic symptoms	Other symptoms	Pretreatment Examination	Treatment
1º Psychiatry service	Low mood and apathy Irritability Psychological distress Asthenia Insomnia Social isolation Hypochondria		Epigastralgia Dyspnea Myalgias Weight loss	Brain CT: N Blood and urine test: N PSA: N RF: N ANA: N ECG: N EEG: N	SNRI NaSSA Lithium BZD (occasionally)
2º Psychiaty service		Instability	Vertigo Weight loss	Cerebral MRI: hemosiderosis signals in different areas	SNRI NaSSA Lithium BZD (occasionally) NL (occasionally)
3º Neurology service	Apathy Irritability Psychomotor restlessness Lack of hygiene Insomnia	Tremor Ataxia Diorentation T and S Hypoprosexia	Weight loss	Cerebral MRI : W/C Rx Thórax: N CT TAP: N Blood and urine test: N Lithium: 1.1 mEq/ l Calcium: N β2Microglobuline: N Serology syphilis and HVI: N Hemoculture mycobacterium: N Mantoux: N	SNRI NaSSA Lithium BZD (occasionally) NL (occasionally)

ANA: Antinuclear antibodies, BZD: Benzodiazepine, CT: Computerized tomography, ECG: Electrocardiogram, EEG: Electroencephalogram, MRI: Magnetic resonance. N: Normal/Negative, NaSSA: Adrenergic α2 and 5-HT2A antagonists, NL: Neuroleptics, PSA: Prostate-specific antigen, RF: Rheumatoid factor, Rx: Radiography, S: Spatial, SNRI: Selective noradrenaline and serotonin re-uptake inhibitors, W/C: Without changes, T: Temporal, TAP: Thoraco-abdomino-pelvic.

aetiologies; a PCR assay for Tropheryma Whipplei on the CSF was ordered. Results were positive, and in order to confirm the diagnosis of WD with CNS involvement a PAS staining of duodenal biopsy diagnostic test was done. Regarding psychopathology, the patient showed a cognitive impairment and a depressive mood with mood congruent psychotic symptoms. In the light of the clinical seriousness and resistance to treatment, it was decided to apply electroconvulsive therapy (ECT). Moreover, it was introduces antibiotic treatment with ceftriaxone (2 g/d) infused intravenously for 2 weeks, followed by oral maintenance treatment with trimethoprim/sulfamethoxazole (TMP-SMX) 320/1,600 mg/d.

After twelve ECT sessions, and once the intravenous antibiotic treatment was finished, clinical impression is of euthymia, symptoms of mental confusion had passed, but there was a persistence of cognitive impairment the moment of medical discharge. Maintenance treatment consisted in a dose of 100 mg of quetiapine before bedtime. Medical follow-up was carried out by the home assistance psychiatry service. During the first year of antibiotic treatment the patient was hospitalized at the psychiatry unit in several occasions due to behavioural disturbance in the context of a significant and progressive cognitive deterioration of cortical functions.

Discussion

Initially the patient was diagnosed of a recurrent depressive disorder, but the deteriorating clinic evolution and the atypical symptoms, led to a diagnosis of WD. Probably, one of the main reasons of diagnosis delay was the fact that he did not present some of the classic symptoms of this illness, such as arthralgias and gastrointestinal manifestations. Moreover, the weight loss, present from the start, is an unspecific and frequent symptoms in patients suffering from cognitive impairment and associated depressive symptoms.

Currently, there are several presentations linked to chronic infection by T. Whipplei, divided into two major groups. Firstly, the most frequent presentation, classic WD marked by histological lesions in the gastrointestinal tract in association with diverse clinical manifestations. Secondly, localized infections without histological digestive lesions such as endocarditis or neurological infection[6,10]. Further-

more, it has also been described acute infections of T. Whipplei, such as pneumonia, gastroenteritis and bacteremia[6].

Neurologic manifestations occur in three situations: neurologic involvement in classic Whipple's disease, isolated WD neurologic involvement, and neurologic relapse of previously treated WD[4]. The neurologic symptoms are various, often complex, and intermingled[28]. The most common neurologic symptoms are cognitive changes (dementia and memory loss) (Table 2), followed by supranuclear ophthalmoplegia, confusion, apathy and psychiatric symptoms; mood symptoms and personality changes predominate among psychiatric manifestations. It should be noted that over 47% of patients with cognitive involvement show psychiatric symptoms[15], as in the reported case. Oculomasticatory myorhythmia and oculo-facial-skeletal myorhythmia, even though less frequents, are considered pathognomic for CNS Whipple's disease[9,15,26]. However, the lack of clinical manifestations does not exclude neurologic involvement[10].

Successful diagnosis can be performed detecting PAS-positive granular, foamy macrophages and the electron microscope study of bacterial invasion at the duodenal biopsy or from other involved body tissues. Nevertheless, other authors consider TW-specific immunohistochemistry and PCR as methods of choice, a useful strategy to measure treatment response and determine treatment maintenance[17,25,27,28].

Regarding treatment, our patient received intravenous ceftriaxone during two weeks, followed by oral treatment with trimethoprim/sulfamethoxazole, that has to be maintained during 1-2 years. This is one of the most recommended manegments[17,29]. However, it has been described the appearance of treatment resistance and illness relapse[10,30]. Due to these findings, the current recommendations suggest bactericidal treatment with a combination of doxycycline and hydroxychloroquine[12,25,31].

Concerning prognosis, neuropsychiatric manifestations generally persist regardless treatment, and are the symptoms that show a more frequent recurrence[9,10,17]; being a frequent cause of death[31]. More favorable outcomes have been described, considering prognostic factors an early diagnosis by PCR and the optimization of treatment[28].

Taking into account the low prevalence of the disease, the variety of signs and symptoms, and their low specificity, diagnosis is usually made at too late stage[16.] This implies the need to consider a large number of

differential diagnosis as in the reported case, where the most common causes of dementia and encephalopathy were ruled out; pharmacological, degenerative, infectious, vascular, autoimmune, tumoral, nutritional and endocrine, until a diagnosis was established.

Table 2 Neurological manifestations of Whipple disease[9]

Manifestations	Prevalence (%)
Supranuclear ophthalmoplegia	32
Dementia	28
Decreasing level of consciousness	27
Memory impairment	25
Confusion	24
Apathy	21
Psychiatric signs	19
Myoclonic sibgs	16
Seizures	14
Nystagmus	14
Upper motor neuron disorder	14
Hypothalamic involvement	11
Cerebellar forms	10
Headaches	10
Myorhythmic forms	8
Hemiparesis	8
Cranial nerve involvement	7
Extrapyramidal movement disorder	7
Peripheral neuropathies	6

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