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Long-term neuropsychiatric sequels in Central nervous system tuberculosis in Mexican patients

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Abstract

Introduction: Central nervous system tuberculosis (CNS TB), the most serious form of TB, is usually associated with an intense neuroinflammatory response and severe sequels, and it is often accompanied by human immunodeficiency virus (HIV) coinfection. Few works have studied mental functioning sequels in this population.

Objective: The aim of this study was to characterize long-term neuropsychiatric sequels in central nervous system tuberculosis (CNS TB) patients and CNS TB/ Human Immunodeficiency Virus (HIV) co-infected patients, and to describe some associated factors.

Methods: Retrospective cohort study in CNS TB patients admitted from 2008 to 2018 in a Mexican neurological center in which sociodemographic, clinical, neuroimaging, cognitive, and neuropsychiatric data were collected. Cognitive sequel data were obtained from a screening tool that has been standardized and normalized for the Hispanic population. Neuropsychiatric data were obtained from the Neuropsychiatric Inventory Questionnaire and from medical records.

Results: A total of 86 subjects were included, 23 had CNSTB and HIV. The mean age was 40.4 years, and 23% of patients had a history of pulmonary TB. The main symptoms were headache, fever, and cranial nerve palsy. Executive functions, visuospatial, and memory impairment were the most common neurocognitive sequels, while the most frequent neuropsychiatric sequels were depression, irritability, and anxiety. There was a correlation between immunity (CD4+ T cell count) and executive functions.

Conclusions: This is the first report in Mexican patients evaluating long-term neurocognitive sequels in CNS TB. Some clinical and sociodemographic traits seem to be neuroprotective factors against long-term neuropsychiatric sequels.

Keywords: CNS-TB; neuropsychiatric sequels; cognitive sequels; HIV

Secuelas neuropsiquiátricas a largo plazo en la tuberculosis del sistema nervioso central en pacientes mexicanos

Resumen

Introducción: La tuberculosis del SNC (TB-SNC), es la forma más seria de TB, usualmente asociada a una respuesta neuroinflamatoria intensa y secuelas severas, además frecuentemente se acompaña de coinfección por virus de inmunodeficiencia humana (VIH). Pocos estudios han estudiado las secuelas mentales funcionales en esta población.

Objetivo: Caracterizar las secuelas neuropsiquiátricas a largo plazo en pacientes con TB-SNC y en pacientes con la coinfección VIH/ TB-SNC, describiendo los factores asociados.

Métodos: Estudio de cohorte retrospectiva en los pacientes con TB-SNC admitidos en un centro neurológico mexicano durante los años 2008 a 2018. Se colectaron los datos sociodemográficos, clínicos, de neuroimagen, cognitivos u neuropsiquiátricos Las secuelas cognitivas fueron obtenidas por herramientas normalizadas y estandarizadas para la población hispánica. Los datos neuropsiquiátricos a través del Cuestionario del Inventario neuropsiquiátrico y de los expedientes clínicos.

Resultados: Se incluyeron un total of 86 sujetos, 23 tenían coinfección VIH/ TB-SNC. La edad promedio fue 40.4 años y 23% de ellos tenían historia de TB pulmonar. Los síntomas clínicos principales eran cefalea, fiebre y parálisis de nervios craneales. A nivel neurocognitivo, las secuelas más comunes implicaron afección de funciones ejecutivas, visuoespaciales y de memoria, mientras que las manifestaciones neuropsiquiátricas más frecuentes fueron depresión, irritabilidad y ansiedad. Se observe correlación entre la inmunidad (conteo de linfocitos T CD4+) y la afección de funciones ejecutivas.

Conclusiones: Este es el primer trabajo evaluando las secuelas neurocognitivas a largo plazo en pacientes con TB en población mexicana. Algunos rasgos clínicos y sociodemográficos parecen ser factores neuroprotectores frente a secuelas neuropsiquiátricas a largo plazo.

Palabras clave: TB-SNC; secuelas neuropsiquiátricas; secuelas cognitivas; VIH.

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Introduction

Central nervous system tuberculosis (CNS TB), the most severe form of tuberculosis (TB), is associated to high mortality and morbidity indices. In fact, surviving TB patients may present chronic neuropsychological sequels even after a successful antituberculous treatment and clinical recovery [1, 2]. Despite the high TB prevalence, information on CNS TB sequels is scanty. Cognitive impairment has been reported because of several infectious diseases, even acute infections unrelated to the CNS[3-5]. The underlying physiopathology has been associated with an activated inflammatory response, which promotes pathogen elimination. However, in some cases these responses persist after the pathogen has been cleared, leading to chronic inflammation and/or neuroinflammation/neurodegeneration[6-7].

Infectious processes show a synergistic, deleterious effect on the cognitive function[8]. In this context, considering that TB is the second most frequent infection worldwide after HIV/AIDS, herein we analyze long-term neuropsychiatric effects in a population of neurological patients. We hypothesized that patients with TB and HIV/AIDS coinfection would show worse cognitive and neuropsychiatric sequels than patients with TB infection alone.

Materials and methods

This retrospective cohort study was conducted at the Instituto Nacional de Neurología y Neurocirugía, a nationwide referral center for neurological diseases for adult patients in Mexico. During a 10-year period, a total of 106 patients with TB diagnosis were admitted to this hospital. However, only 86 patients (63 TB infection alone and 23 TB/HIV-AIDS coinfection) were included in this report.

Demographic, clinical, and neuroimaging characteristics, as well as neuropsychological and neuropsychiatric evaluation data, were recorded for all patients.

CNS-TB diagnosis was based on the Marais criteria, which classify each case as a definite, probable, or possible diagnosis [9]. Disease severity assessment was based on the British Medical Research Council criteria; this staging system has some prognostic value in medical and functional recovery. Briefly, this criterion set takes into consideration the Glasgow coma score and the presence of focal neurological deficits[10].

Adult patients >18-year-old, both sexes with CNS-TB definitive and probable according to Marais criteria with and with HIV coinfection were considered to participate. Only those with complete electronic or physic medical records and neuropsychological and neuropsychiatric evaluation were included.

Neuropsychological and neuropsychiatric evaluation

The patients included in this study were subjected to a MoCA and a NEUROPSI test, and to the Neuropsychiatric Inventory Questionnaire.

The MoCA test, a free screening tool to identify cognitive impairment, has already been standardized for the Mexican population [11]. This test evaluates the global cognitive state, executive functions, visuospatial ability, memory attention, concentration and working memory, as well as language and orientation, with a maximum score of 30 points.

The Neuropsychiatric Inventory Questionnaire is one of the most common measures to assess neuropsychiatric symptoms in a brief screening informant-based questionnaire. It assesses the presence and severity of twelve neuropsychiatric symptoms, including delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep and nightmare behavior change, and appetite/eating change, and the distress each one causes on the caregiver [12,13]. This questionnaire was applied to most subjects in our study. In addition, we sought for and collected data on neuropsychiatric symptoms in the medical records from the Neuropsychiatry Service in our center. Only the frequency of patients with each neuropsychiatric sequel was recorded.

Finally, the NEUROPSI test, a screening test that has been standardized and validated for the Hispanic population, assesses orientation in person, time and space, attention and concentration in verbal and visuospatial modalities, memory in immediate and delayed recall in both modalities, language (naming, comprehension, repetition, and fluency), reading, writing and executive functions including both problems solving (abstraction and categorization) and several motor programming tasks. This test allows for assessing subjects aged 16 to 85 years, with different education levels (0 to 24 years of study). It also gives a cognitive profile of the subject, whose performance can be classified as high, normal, moderate impairment, or severe impairment [14]. This evaluation was performed by neuropsychologists of the Behavior and Cognition Unit of the Instituto Nacional de Neurología y Neurocirugía.

Ethics statement

The Ethics Committee in our Institution approved the protocol of this study (permit No. 33/20). This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all Mexican regulations: Ley General de Salud en Materia de Investigación para la Salud (Título V, capítulo único, Arts. 96-103) and Norma Oficial Mexicana NOM-012-SSA3-2012.

Statistical analysis

Qualitative variables were expressed as percentages and compared using the X^2 distribution. Differences were considered as statistically significant at $P < 0.05$. Quantitative variables are reported as mean ± standard deviation. Either a two-tailed Student's *t* or a Mann-Whitney test was used for comparison between our series, depending on the results in the Kolmogorov-Smirnov test.

Correlation analysis

Spearman's rank correlation coefficient was used to assess the correlation between neuropsychological/neuropsychiatric sequels and the CD4+ T cell count in HIV/AIDS group. The statistical significance was set as $P < 0.05$. All data were recorded in MS Excel and analyzed in SPSS v.21 (IBM Inc., Armonk, NY).

Results

General characteristics of population is summarized in the table 1.

Clinical and neuroimaging characteristics

According to the diagnostic criteria proposed by Marais et al. (2010), 24 (27.6%) patients had a definite diagnosis, 47 (54%) were probable TB cases, and 15 (17.4%) were possible TB cases. Those cases with a non-definite diagnosis were confirmed by the clinical and radiological response to empirical antituberculous treatment.

The mean age of the population under study was 40.4 ± 15.8 years, and the mean education time was 8.9 ± 4.1 years. The mean time of symptom evolution was 62.5 ± 79.8 days. Among the 86 patients studied, 20 had pulmonary TB. The main symptoms were headache in 67 patients (77.9%); vomiting, diaphoresis, and nausea in 60 (69.8%); fever in 46 (53.4%); and cranial nerve palsies in 44 (51.2%). Upon hospital admission, 19 patients (22%) were in stage I, 60 (69.7%) were in stage II, and 7 (8.1%) were in stage III according to the British Medical Research Council clinical criteria (Table 2).

Magnetic resonance imaging (MRI) performed in the acute phase of the disease showed abnormalities in 70 patients (81.4%): 11 patients (12.7%) had hydrocephalus, 40 (46.5%) showed basal meningitis, and 18 (20.9%) had vasculitis. MRI results of a representative case of CNS TB alone and a CNS TB/HIV coinfection case are shown in Figure 1.

In the HIV/AIDS coinfection group, the mean viral load was 251269.50 ± 401153.72, while the mean CD4+ T lymphocyte count was 197.06 ±173.5.

Neuropsychological and neuropsychiatric performances

The mean clinical follow-up duration was 21.6 months (range: 3-119). On neuropsychological evaluation, executive functions ("sequences") were the most frequently affected domain, in 27.2% of patients; selective attention ("visual detection") was impaired in 22.7%, visuospatial memory evocation in 22.7%, and motor programming ("opposite reactions") in 22.7%. Additionally, 18.2% of patients had impaired

Table 1. Sociodemographics and clinical characteristics of the retrospective cohort

	All patients (N=86)	CNS-TB (N=63)	HIV/AIDS and CNS-TB(N=23)	P
	M (S.D)	M (S.D)	M (S.D)	
Age	40.43 (15.8)	43.60 (17)	31.74 (6.6)	**.004***
Escolarity (years)	8.94 (4.1)	8.50 (4.1)	10.13 (4)	**.036***
Time of disease evolution before hospital admission (days)	62.58 (79.8)	68.62 (86.94)	46.04 (54)	.278
Time of clinical follow-up (months)	21.62 (27.6)	23.7 (33.4)	17.43 (9.5)	.443
Sex: Female/Male	26/60	26/37	0/23	**.000***
History of pulmary TB	20 (23.3%)	13 (20.6%)	7 (30.4%)	.341
History of febril syndrome	46 (53.4%)	33(52.3%)	14 (60.9%)	.447
History of consuntive syndrome	29 (33.7%)	17 (26.9%)	12 (52.1%)	**.029***
Smocking	36 (41.9%)	23 (36.5%)	13 (56.5%)	.096
Alcoholism	49 (57%)	29 (46%)	20 (86.9%)	**.001***
Malnutrition	10 (11.6%)	7 (11.1%)	3 (13%)	.805
Diabetes mellitus	16 (18.6%)	15 (23.8%)	1 (4.3%)	**.040***
Arterial hypertension	23 (26.7%)	15 (23.8%)	8 (34.7%)	.309
Clinical symptoms Headaches	67 (77.9%)	52 (82.5%)	15 (65.3%)	.087
Meningeal syndrome	35 (40.7%)	29 (46%)	6 (26%)	.096
All neurologic symptoms	60 (69.8%)	47 (74.6%)	13 (56.5%)	.106
Cranial nerve involvement	44 (51.2%)	33 (52.3%)	11 (47.8%)	.708
Seizures	26 (30.2%)	18 (28.5%)	8 (34.7%)	.579
Altered conciousness	31 (36%)	20 (31.7%)	11 (47.8%)	.169
Intracranial hypertension	19 (22.1%)	16 (25.3%)	3 (13%)	.222

Numerical variables show means and standard deviation: M (S.D).

The P-value shows the intergroup significance for continuous variables performed with the Mann-Whitney U test, and the intergroup significance for dichotomous variables performed with the Chi-square test.

* Statistically significant P values (P<.05).

Table 2. British Medical Research Council (BMR) Tuberculosis score and Charlson comorbidity index

		All patients (N=86)	CNS-TB (N=63)	HIV/AIDS and CNS-TB(N=23)	P
		N (%)	N (%)	N (%)	
BMR	I	19 (22%)	15 (23.8%)	4 (17.39%)	.525
	II	60 (69.76%)	41 (65.07%)	19 (82.61%)	.117
	III	7 (8.13%)	7 (11.11%)	0 (0%)	.095
Charlson Comorbidity Index	0	31 (36%)	31 (49.2%)	0 (0%)	<.0001*
	1	14 (16.3%)	14 (22.2%)	0 (0%)	
	2	10 (11.6%)	10 (15.8%)	0 (0%)	
	3	6 (7%)	6 (9.5%)	0 (0%)	<.0001*
	4	1 (1.2%)	1 (1.5%)	0 (0%)	
	6	22 (25.6%)	1 (1.5%)	21 (91.3%)	
	7	2 (2.3%)	0 (0%)	2 (8.7%)	

The total number of cases and the percentage of the sample it represents are shown N (%).
The P-value shows the significance between groups in the variables with the Chi-square test.
*Statistically significant P-values (P<.05)

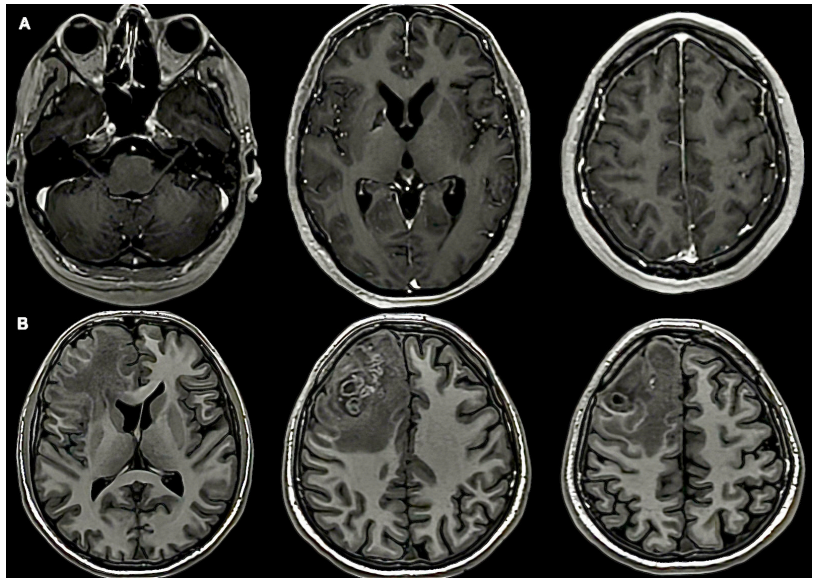

Figure 1. Magnetic resonance images of central nervous system tuberculosis patients.
(A) Central nervous system tuberculosis-infected patient: Axial contrast-enhanced T1 magnetic resonance images of the brain showing a basal hyperintense inflammatory exudate reaching the brain convexity (pachymeningitis), leptomeningeal enhancement, and hydrocephalus. Volumetry report (data not shown) revealed right striatum, right globus pallidus, left hippocampus, and right amygdala volumes under the expected limits.
(B) Central nervous system tuberculosis/HIV co-infected patient: Axial non-contrast T1 magnetic resonance images reveal parenchymal tuberculomas on the right frontal lobe with perilesional edema and deviation of midline structures. The volumetry report (data not shown) indicated left cerebrum volume under the expected limits.

visuoconstructional skills and visuospatial memory encoding, short-term verbal memory ("delayed free recall, cueing retrieval and recognition format"), and language ("repetition and phonologic verbal fluency"). On neuropsychiatric evaluation, the most frequent symptoms were depression in 15.1% patients, irritability in 11.6%, and anxiety in 9.3%.

Considering that executive functioning deficits have been also reported in depression we analyzed if this clinical characteristic is a modifier of the cognitive outcome associated with TB and TB/HIV coinfection[15,16]. Complementary Chi-square analysis was performed not statistically differences with executive dysfunction and depression (X^2 = 0.60; P = 0.793), neither with antiretroviral treatment and depression (X^2 = 0.28; P = 0.867) were found.

Correlation between cognitive function and immune response in HIV/AIDS patients

A Spearman correlation analysis was performed to evaluate the impact of the immune response on cognitive features (the immune response status was determined by the CD4 + T lymphocyte count on admission time). Positive correlations were found between executive function ("calculation abilities": r = 0.892, P = 0.042 and "similarities": r = 0.851, P = 0.032) and CD4 + T cell count; on the other hand, a statistical trend was observed in language comprehension (r = 0.772, P = 0.072).

Correlation between neuropsychiatric sequels and immune response in HIV/AIDS patients

A Spearman correlation analysis was performed to evaluate the impact of the immune response on neuropsychiatric sequels; the immune response status was determined by the CD4 + T cell count on admission time. No significant correlations were found.

Neuropsychological and neuropsychiatric evaluation in TB alone and HIV/AIDS-TB coinfected patients

The patients were distributed into two groups based on their HIV coinfection status, CNS TB alone group and CNS TB/HIV coinfected group. On neuropsychological evaluation, TB/HIV coinfected patients performed significantly better than TB infected patients in visuospatial memory evocation (P = 0.038). No significant differences in neuropsychiatric symptoms were observed between groups. (Figure 2).

Discussion

CNS TB is strongly associated with acute mental function disorders, and chronic sequels are usual even after medical recovery[1,6,17]. While the pathophysiology of these cognitive and behavioral sequels remains unclear[1], it has been associated with acute neuronal death triggered by the pathogen and/or the innate and adaptive immune response. In fact, both response types can persist in time upon the absence of the pathogen that originally caused chronic dysfunctions[6].

Based on the reports in the literature, we hypothesized that the CNS TB outpatients would show a higher prevalence of cognitive impairment. In our series, 18/22 patients (81.9%) who were neuropsychologically evaluated showed at least one abnormal execution domain in some NEUROPSI subtests; these results corroborate the already reported prevalence of cognitive sequels in CNS TB patients[1,2,18-20]. The highly variable prevalence of cognitive impairment in these series is associated with the neuropsychological instrument used, the mean follow-up period, and sample characteristics[21].

In our study, the most affected cognitive domains were executive functions, visuospatial functions, and memory in immediate and delayed recall. These results coincide with previous studies in patients with tuberculous meningitis[1,20].

On neuropsychological evaluation, our patients showed a worse performance in the "sequences" subtest; in this item, subjects must activate prefrontal cortex networks including the dorsolateral prefrontal cortex[22], because the subtest demands the perception and execution of a logical sequence, alternating visual elements.

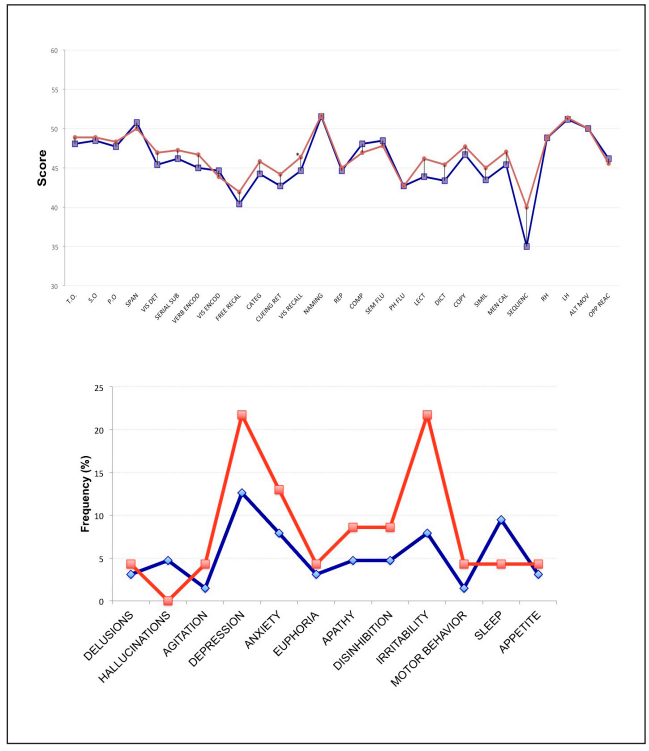

Figure 2. Long-term sequels: comparison between groups.
(A) Cognitive evaluation: the cognitive performance score of CNS TB (alone) patients in each NEUROPSI subtest is shown in blue. The cognitive performance score of CNS TB/HIV (co-infected) patients in each NEUROPSI subtest is shown in red. Data points and error bars indicate mean and SD values, respectively. Only visual memory evocation showed statistically significant differences (P < 0.05), according to the Mann-Whitney test.
(B) Neuropsychiatric evaluation: The frequency (as a percentage) of neuropsychiatric disorders in CNS TB/VIH co-infected patients are shown in red. The frequency (as a percentage) of neuropsychiatric disorders in CNS TB-infected patients is shown in blue. No statistically significant differences were observed, according to the X^2 test.

On the other hand, we found impairment in the target cancelation task, which is frequently associated with visual selective attention. In qualitative terms, our patients suffered from omission- rather than distortion-related mistakes. Because of the nature of the task, this impairment could have several causes: it could be an impairment in visual scanning or a global slowing. Unfortunately, the retrospective nature of our analysis did not provide us with more detailed qualitative data; thus, further research is required to better understand these results.

The opposite reactions task can be considered as a modification of the go/no-go task developed by Alexander Luria[22] which assesses motor inhibition[23]. In NEUROPSI, the patients must raise one finger in response to a fist and a fist in response to a finger; thus, this finding suggests impairment in inhibition processes associated to fronto-striatal-pallidal loops[24].

With respect to visuospatial skills, our cases showed distortion and omission mistakes. This kind of impairment has been associated with damage in the bilateral inferior longitudinal fasciculus, parahippocampal gyrus, and visual association areas that carry out the extraction and integration of objects' characteristics[20].

In memory deficits, impairment was observed in delayed recall in verbal and visual modalities. In the verbal modality, all patients suffered from a severe impairment. In most patients, this impairment improved after providing semantic cues for retrieval, suggesting alterations on frontal circuits involving the dorsolateral prefrontal cortex, as well as diencephalic structures, which are commonly damaged by secondary vasculitis induced by inflammatory exudates and microglial reaction (border zone encephalitis) in CNS TB[20,25,26].

Interestingly, in our cases we found some improvement in the recall after giving recognition items to all patients, suggesting a better compensation from entorhinal cortex circuits associated with long-term consolidation memory and recognition TB[27] in comparison with prefrontal lobe circuits. Nevertheless, more studies are required to confirm this initial hypothesis.

Our patients also exhibited impairment in phonologic word fluency task. This kind of task is sensitive to medial frontal damage due to a reduced initiation and production of responses. This task also involves planning, language processing, and searching, and is sensitive to lateralized left dorsolateral prefrontal cortex damage TB[22]. Finally, we also found a high prevalence of impairment in language repetition, which often occurred when repeating long sentences, suggesting impairment in the memory span, rather than a failure in repetition itself.

In contrast with the report by Hestad et al.[28], we did not find a more severe cognitive impairment in patients with TB/HIV with respect to patients with TB alone; instead, we found a better performance in coinfected patients, possibly because of the younger age and higher education level in TB/HIV patients, which increase the cognitive reserve[29-31].

The British Medical Research Council staging test has shown that advanced impairment stages upon hospital admission predict a clinical worsening and provide a long-term functionality prognosis[1,32]. In our series, no patients with CNS TB/HIV were in stage III or higher upon admission. Therefore, sociodemographic and disease severity features on admission time are associated with long-term cognitive impairment as reported in Chen et al.[1] The neuroprotective effect of these features seems to be stronger than the chronic neuroinflammation caused by both infections (TB and HIV) and by the neurotoxic effect associated to antiretroviral and antituberculous drugs[33,34].

Several studies have reported an association between immune function and cognitive performance. In this context, our study showed that some clinical features, like CD4+T lymphocyte count on admission, are associated with long-term cognitive sequels, specifically with "calculation abilities" of the executive function domain; this suggests that a robust immune response is protective from cognitive impairment in CNS TB patients.

Additionally, most of our HIV/AIDS patients had a CD4+ T lymphocyte count > 250, as measured on the closest date before neuropsychological evaluation (data not shown). Therefore, in addition to the clinical and sociodemographic characteristics already mentioned, the status of the immune response must be taken into consideration when assessing the cognitive function of patients with HIV-associated infections, such as TB.

Previously, emotional disturbances were reported as the most prevalent neuropsychiatric symptom in CNS TB patients[35]. Our series showed similar results; in fact, depression was the most frequent neuropsychiatric sequel, being reported in 15.1% of our patients. In this regard, the American Psychiatric Association estimates a depression prevalence of 7% in the general population[36]. Our results suggest that CNS TB patients have a higher risk of suffering from depression than the general population. This increased risk was previously reported by Duko et al[37]. Depression is associated with increased levels of pro-inflammatory cytokines, which can up-regulate various enzymes, including indoleamine 2, 3-dioxygenase (IDO) of the tryptophan-kynurenine pathway, decreasing serotonin synthesis[38]. Neurobiological correlations indicate that abulia, apathy, and a reduced activity are related to ventromedial prefrontal cortex damage [39]; these symptoms can be observed in depression, which is also associated to damage in the entorhinal cortex and cingulate gyrus[40]. With respect to other symptoms, irritability and impulsiveness are also highly prevalent in CNS TB patients. In fact, both sequels are associated with damage in orbitofrontal cortex networks[38] connected with the limbic system. These features indicate a major disorganization and impairment in behavior planning, which are expressed both on neuropsychiatric and cognitive sequels.

As previously reported, anxiety has a high prevalence in TB patients[37]. Anxiety is associated with brain circuits that include the orbitofrontal cortex and limbic system structures, specifically the amygdala[41].

TB/HIV coinfection is a known risk factor to develop depression and anxiety among TB patients[37]. Considering this and the neuroinflammation associated with HIV and TB, we hypothesized that the coinfection group would show a worse neuropsychiatric status; however, no statistical differences were found in any neuropsychiatric symptom between both groups. These findings can be explained by the retrospective characteristics of this study, like the reporting or evaluation dates of neuropsychiatric symptoms. It was previously reported that TB/HIV patients showed some improvement in neuropsychiatric assessment throughout their disease, with neuropsychiatric signs decreasing in prevalence and severity, from severe during intensive treatment to mild in the follow-up[42]. Finally, it should be noted that there no statistical differences were observed in the prevalence of depression, irritability, nor impulsiveness between groups, while anxiety increased in coinfected patients in our small series, so it could be advisable to increase the sample size.

The correlation between the immune response and the occurrence of psychiatric manifestations has shown overlapping results[43]. In our series, we did not find significant differences, neither with respect to the CD4+ T cell count on admission time nor shortly before neuropsychiatric assessment. Nevertheless, there is a growing body of evidence of the role of inflammation in the development of psychiatric conditions, supported by findings on clinical improvement inflammation markers are regulated[44,45].

The neural correlates of the cognitive and neuropsychiatric sequels mentioned above are in agreement with the pathophysiology of CNS TB. Indeed, diencephalic structures and basal ganglia are frequently affected by ischemia because of CNS TB on lateral lenticulostriate, medial lenticulostriate, and posterior thalamoperforating arteries[26] (Figure 1). The prefrontal cortex has several functional networks linked to the limbic system, subcortical structures, and other cortices[22]. Schizophrenia is another neuropsychiatric condition in which inflammation is known to play a role. Several studies have shown the overexpression of mRNA of pro-inflammatory cytokines (IL-6 and IL-8) in the dorsolateral prefrontal cortex in patients with schizophrenia[46]. As the disease evolves, there is a decrease in the mRNA levels of pro-inflammatory cytokines, which may be related to the anti-inflammatory effect of antipsychotic drugs[46,47]. Considering data from other CNS conditions, we suggest that cognitive and neuropsychiatric impairment in patients with CNS TB is caused by chronic neuroinflammation, and that the stabilization of symptoms that occurs as the disease progresses[42] may be due a decrease in the inflammatory response.

To our knowledge, this is the first study in a Mexican population considering long-term neuropsychiatric sequels in CNS TB patients. This work is an initial approach in the country, and one of the first in the world. One strength of this work is the access to several clinical characteristics, neuropsychological and neuropsychiatric evaluations, often inaccessible in other studies, which allowed us to analyze the relationship between cognitive and neuropsychiatric sequels and their associated factors.

Limitations

This study is mainly limited by its retrospective nature, the small number of patients who met inclusion criteria, and possible bias conditioned by non-rutinary neuropsychological evaluation in TB population (these are performed when cognitive complains are referred by the patient or family member or when treating physician found cognitive impairment in the basic neurological examination). Our hospital as a national reference center is affected by a significant saturation which limits the patient's timely access to neuropsychological or neuropsychiatric evaluations. Furthermore, neuropsychiatric conditions are often underreported, and may lead to underdiagnosed sequels.

In conclusion the cognitive and neuropsychiatric sequels observed in our TB patient series suggest functional alterations in the cortico-subcortical temporal and frontal networks, which originate cognitive deficits in executive, visual-spatial, and memory functions, as well as emotional and mood neuropsychiatric sequels. Therefore, based on neuroanatomical correlates, there is a close relationship between cognitive and neuropsychiatric sequels in patients with CNS TB. Educational level and age, illness severity on admission, and immune response status seem to be neuroprotective factors for cognitive and neuropsychiatric sequels.

Ethical considerations

Conflicts of interest. The authors declare that no conflict of interest exists.

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