Cognitive impairment in patients with central nervous system tuberculosis

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Abstract

Introduction: Tuberculosis (TB) in Mexico remains an important cause of morbidity and mortality; in the past 4 years, 110,681 cases of pulmonary tuberculosis and 1571 cases of tuberculous meningitis were reported. **Objective:** To determine the neurocognitive sequelae, clinical presentation and neuroimaging alterations in patients with central nervous system tuberculosis. **Methods:** A retrospective, analytical, and cross-sectional study was carried out from 2010 to 2019. Patients with central nervous system tuberculosis, with and without HIV/AIDS coinfection, were included. **Results:** During the study period, 104 cases with a definitive or probable central nervous system tuberculosis diagnosis were included; 38% had HIV/AIDS coinfection, and 55%, various comorbidities ($p = 0.0001$); 49% had cognitive alterations, and 14% died. **Conclusions:** Although HIV/AIDS infection can contribute to cognitive decline in patients with tuberculous meningitis, no differences were observed between patients with and without HIV/AIDS. Cognitive sequelae showed improvement during follow-up with adequate management and therapeutic control of the patients.

KEY WORDS: Cognitive impairment. Cognitive sequelae. Tuberculous meningitis. Central nervous system. HIV/AIDS.

Deterioro cognoscitivo en pacientes con tuberculosis del sistema nervioso central

Resumen

Introducción: La tuberculosis en México sigue siendo causa importante de morbimortalidad; en los últimos cuatro años, se reportaron 110 681 casos de tuberculosis pulmonar y 1571 casos de tuberculosis meníngea. **Objetivo:** Determinar las secuelas neurocognoscitivas, presentación clínica y alteraciones en los estudios de neuroimagen en pacientes con tuberculosis del sistema nervioso central. **Métodos:** Se realizó un estudio retrospectivo, analítico y transversal de 2010 a 2019. Se incluyeron pacientes con tuberculosis del sistema nervioso central, con y sin coinfección por VIH/sida. **Resultados:** Durante el periodo de estudio se incluyeron 104 casos con diagnóstico definitivo y probable de tuberculosis del sistema nervioso central; de acuerdo con los criterios de Marais, 38 % presentó coinfección por VIH/sida y 55 %, diversas comorbilidades ($p = 0.0001$); 49 % presentó alteraciones cognoscitivas y 14 % falleció. **Conclusiones:** Aunque la infección por VIH/sida puede contribuir al deterioro cognoscitivo del paciente con tuberculosis meníngea, no se observaron diferencias entre pacientes con y sin VIH/sida. Las secuelas cognoscitivas mostraron mejoría en el seguimiento con el adecuado manejo y control terapéutico de los pacientes.

PALABRAS CLAVE: Deterioro cognitivo. Secuelas cognitivas. Tuberculosis meníngea. Sistema nervioso central. VIH/sida.

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Introduction

Today, tuberculosis (TB) is a major health problem worldwide owing to its high mortality. It is one of the ten leading causes of death and the first caused by a single infectious agent, whereby it surpasses HIV/AIDS infection. In this context, during 2018, 10 million people were estimated to be affected by TB in the world, which caused 1.2 million deaths in people without HIV infection and nearly 251,000 in people with HIV/AIDS.¹ Central nervous system TB, particularly meningeal involvement, is the most serious and potentially fatal of all forms of extra-pulmonary involvement.² In surviving patients, neurological sequelae are diverse, including motor and sensory disorders, hydrocephalus and cognitive impairment,³⁻⁵ which includes a gradual and progressive loss of mental functions in the domains of memory, orientation, abstraction, language, reasoning, executive functions, and learning and visuospatial skills.^{6,7} Although it is a multi-causal entity, systemic and central nervous system infections appear to play an important role, including HIV/AIDS infection.^{8,9}

In Mexico, there is no information on neurological sequelae in patients with meningeal TB,¹⁰ particularly on cognitive impairment, which is why we decided to carry out a 9-year analytical, cross-sectional, retrospective study in patients admitted to a neurological referral center, with the purpose to evaluate mental functions compromise and cognitive impairment at hospital discharge (early involvement) and at 12 months of clinical follow-up (long-term); in addition, the possible risk factors of said population were evaluated.

Methods

A retrospective, analytical, cross-sectional study was carried out in adult patients cared for at the National Institute of Neurology and Neurosurgery from 2010 to 2019. Marais et al. Meningeal TB Diagnostic Consensus criteria were used;¹¹ only patients aged ≥ 15 years with a definitive diagnosis and those with probable diagnosis and clinical-radiological response to empirical treatment with antitubercular medications were included.

During hospitalization, patients were applied the Montreal Cognitive Assessment (MoCA) test and neuropsychological tests (NEUROPSI) in order to assess short-term memory, visuospatial skills, executive

functions, attention, concentration and working memory, language and spatiotemporal orientation.

All qualitative variables were expressed as percentages, and their comparison was carried out using the chi-square test. Statistically significant differences were those with a p-value < 0.05 . Similarly, quantitative variables were expressed as means $\pm$ standard deviations. Student's t-test or Mann-Whitney's U-test were used, depending on the behavior, for comparisons with Kolmogorov–Smirnov test. All data were analyzed with the SPSS program, version 22.

The research was approved by the Research Ethics Committee of the National Institute of Neurology with registration number 96/17.

Results

During the study period, 118 patients with clinical features suggestive of TB were detected, but only 104 met the inclusion criteria. These patients were cared for at the National Institute of Neurology and Neurosurgery.

Population epidemiological characteristics

Thirty-nine patients (38%) with meningeal TB and HIV/AIDS coinfection and 65 (63%) without HIV coinfection were included. Table 1 summarizes groups general characteristics. Patients in the group with HIV/AIDS were significantly younger ($p = 0.04$). Median HIV viral load (at HIV infection diagnosis) was 1,111,944 (interquartile range [IQR] = 476,822), while median HIV viral load at TB diagnosis was 69,055 (IQR = 196,749). Regarding lymphocyte subpopulations, median CD4+ T lymphocytes (at HIV diagnosis) was 111/mm³ (IQR = 198), whereas at TB diagnosis it was 126/mm³ (IQR = 208).

According to Marais et al. criteria,¹¹ in our population, a definitive diagnosis was observed in 30% and a probable diagnosis in the rest, although with clinical and radiological adequate response to anti-tubercular medications.

Clinical characteristics

In the overall population, the most common clinical presentation was meningitis (62%, $n = 64$) and hydrocephalus (5%, $n = 5$). Other manifestations (cognitive impairment, secondary vasculitis, etc.) were observed in 34% ($n = 35$). There were no statistically significant

Table 1. General characteristics of the groups

Characteristic	Meningeal TB				p-value
	HIV/AIDS coinfection (n = 39)		No HIV coinfection (n = 65)		
Age in years, median (IQR)	31 (10)		40 (27)		0.04
	N	%	n	%	
Gender					0.0001
Males	37	95	35	54	
Females	2	5	30	46	
Origin					0.06
Mexico City/metropolitan area	24	62	27	42	
Other state	15	38	38	58	
History of pulmonary TB	6	2	8	1	0.7
Comorbidities	39	68	18	32	0.0001
Clinical presentation					0.09
Meningitis	20	51	44	68	
Hydrocephalus	2	5	3	5	
Other	17	44	18	28	
Clinical outcome					0.0001
Survival	32	82	57	89	
Death	7	18	7	11	

IQR: interquartile range.

differences in clinical presentation between patients with and without HIV/AIDS coinfection. The state of consciousness, evaluated using the Glasgow coma scale, had an average score of 14 ± 2.2 at admission in the entire population, and at discharge, 13.3 ± 4.4 .

Neuroimaging features

All patients underwent magnetic resonance imaging (MRI), with the main findings being meningitis or leptomeningeal enhancement (n = 31, 24%), abscesses or collections (n = 38, 29%), ischemia/infarcts (n = 6, 4.6%) and hydrocephalus (n = 5, 5%). Secondary vasculitis was reported in 33 patients (25%) by transcranial Doppler ultrasound.

Complementary studies

In all cases, bacteriological cultures were processed in Lowenstein-Jensen medium; however, isolation was only achieved in 21 patients (20%), as determined in biological samples: cerebrospinal fluid in five cases (23%), bronchial secretion in six (29%) and urine in 10 (48%). GeneXpert cerebrospinal fluid PCR test was positive in 15 patients (13%). Cerebrospinal fluid cytochemical examination showed characteristics of

inflammation, and cellularity was higher in the group with HIV coinfection ($p = 0.03$). No significant differences were identified between groups in terms of adenosine deaminase (ADA) levels at admission or during clinical follow-up (Table 2).

Neurocognitive evaluation

Neurocognitive alterations were found in our population, including significant short-, mid-, and long-term memory loss; as well as loss of thinking ability, judgment, and executive skills and verbal fluency alteration, and even mood alterations, with regard to which mild depression predominated according to evaluation with the MoCA and NEUROPSI tests. MoCA assessment was carried out at hospital admission and during outpatient follow-up before and after 12 months post-discharge. At hospital admission, mean score in patients with HIV/AIDS coinfection was 23.4 ± 5.7 ; on follow-up evaluation before 12 months, it was 24.3 ± 4.4 ($p = 0.01$), and after 12 months, it was 26.6 ± 0.5 ($p = 0.02$); patients without HIV coinfection showed a score of 24.1 ± 5.3 at admission, 23.7 ± 5.6 on follow-up before 12 months, and 24 ± 7.1 after 1-year follow-up.

Visuospatial alteration was observed in 16 patients (41%) with HIV/AIDS coinfection, as well as identification

Table 2. Complementary studies and CSF analysis characteristics

Characteristic	Meningeal TB				p-value
	HIV/AIDS coinfection (n = 39)		No HIV coinfection (n = 65)		
	Median	IQR	Median	IQR	
CSF cytochemistry at meningeal TB diagnosis	44	24	45	47	0.7
Glucose (mg/dL)	81	159	115	1594	0.4
Protein (mg/dL)	37	125	96	298	0.03
Cells/mm ³					
Admission ADA (IU/L)	7	13	7	12	0.4
Follow-up ADA (IU/L)	4	7	3	9	0.5

IQR: interquartile range; CSF: cerebrospinal fluid, ADA: adenosine deaminase.

alteration in six (15.4%), language alteration in 12 (30.8%), abstraction alteration in 12 (30.8%), memory alteration in 20 (51.3%) and orientation alteration in 13 (33.3%). In the group without HIV coinfection, visuospatial alterations were observed in 23 patients (37.7%), identification alteration in eight (13.1%), language alteration in 17 (27.4%), abstraction alteration in 16 (25.8%), memory alteration in 30 (47.3%) and orientation alteration in 16 (25.8%). There were no statistically significant differences between groups (Table 3).

Attention was found to be more frequently altered in patients with HIV/AIDS coinfection (26 cases, 66.7%), which translated into statistically significant relevance ($p = 0.02$).

There were no significant differences in the degree of impairment severity between groups; however, patients in whom manifestations started with neurocognitive deterioration alterations at hospital admission were more prone to develop subsequent permanent alterations ($p = 0.001$).

Treatment

All patients received DOTBAL (rifampicin, pyrazinamide, ethambutol and isoniazid), pyridoxine and dexamethasone 0.3 mg/day for three weeks, with subsequent de-escalation with oral prednisone during hospitalization. Antitubercular treatment intensive phase consisted of 60 doses, while the maintenance phase lasted 15 to 18 months, according to neuroimaging findings.

Among 104 patients who received empirical treatment, 70% had a favorable response (clinical and radiological) to it.

Treatment effectiveness had no relevance in the presence of cognitive impairment ($p = 0.4$),

deterioration severity degree ($p = 0.2$) or appearance of sequelae at discharge ($p = 0.3$).

Discussion

Meningeal TB continues to have a high mortality rate, and thus constitutes an alarming public health problem.¹² In this research, very few patients had active pulmonary TB or a history thereof at diagnosis; at the same time, few patients had HIV as a risk factor, unlike what is documented in the literature.¹³ Clinical manifestations and findings on imaging studies were similar to those described in other investigations, predominantly data consistent with meningitis and collections.^{14,15}

No statistical relevance was recorded in clinical presentation, imaging findings or cerebrospinal fluid inflammatory characteristics in patients with or without HIV/AIDS coinfection.

Multiple studies in the literature have demonstrated that cognitive deterioration in people with HIV is closely related, most notably in people who are not yet on treatment.¹⁶ Efficacious antiretroviral treatment exponentially delays cognitive impairment.¹⁷

Cognitive impairment was slightly higher in patients with HIV/AIDS (51.3%) than in patients without HIV coinfection (47.7%); however, in patients with HIV/AIDS, moderate impairment (55%) was predominant, and in patients without HIV, severe impairment (58.1%). Cognitive sequelae occurred in both groups, with no differences.

Even when central nervous system TB in patients with HIV/AIDS is associated with a higher risk of cognitive impairment, no higher degree of severity or sequelae were demonstrated in these patients. During follow-up, improvement of previously defined sequelae was observed in both groups (with and without HIV infection), with higher scores in patients with HIV/AIDS.

Table 3. Alterations, severity and cognitive sequels according to MoCA test

Variable	Meningeal TB				p-value
	HIV/AIDS coinfection (n = 39)		No HIV coinfection (n = 65)		
	Mean ± SD		Mean ± SD		
MoCA					
Admission	23.4 ± 5.7		24.1 ± 5.3		0.9
< 12-month follow-up	24.3 ± 4.4		23.7 ± 5.6		0.01
> 12-month follow-up	26.6 ± 0.5		24 ± ≥ 7.1		0.02
	n	%	n	%	
Visuospatial alteration					
Yes	16	1	23	37.7	0.7
No	23	59	38	62.3	
Identification alteration					
Yes	6	15.4	8	13.1	0.7
No	33	84.6	53	86.9	
Attention alteration					
Yes	26	66.7	27	43.5	0.02
No	13	33.3	35	56.5	
Language alteration					
Yes	12	30.8	17	27.4	0.7
No	27	69.2	45	72.6	
Abstraction alteration					
Yes	12	30.8	16	25.8	0.5
No	27	69.2	46	74.2	
Memory alteration					
Yes	20	51.3	30	47.3	0.7
No	19	48.7	32	52.7	
Orientation alteration					
Yes	13	33.3	16	25.8	0.4
No	26	66.7	46	74.2	
Cognitive impairment					
Yes	20	51.3	31	47.7	0.7
No	19	48.7	34	52.3	
Cognitive sequels					
Yes	21	58.3	38	60.3	0.8
No	15	41.7	25	39.7	
Severity					
Moderate	11	55	13	41.9	0.3
Severe	9	45	18	58.1	
Overall population	Cognitive impairment		No cognitive impairment		
Sequels at discharge	36	76.6	23	44.2	0.001

Limitations of our research lay in the impossibility to collect missing data in medical records, given that this was a retrospective study; in the absence of long-term follow-up, since continuing with 100% of the patients was not possible due to patient deaths and non-attendance at outpatient control visits; as well as in the sample size. In view of the above, for the scope of this investigation to be improved, it should be

carried out in a larger population; therefore, a national multi-center study would be really enriching.

Conclusions

In this retrospective, analytical, cross-sectional study, we report neurocognitive alterations in a Mexican population with central nervous system TB with

and without HIV coinfection. Clinical, imaging and laboratory manifestations corresponded to those described in national and international investigations carried out over the past decade.¹⁸⁻²¹ There were no data consistent with a statistically significant relationship between cognitive impairment and HIV coinfection, probably due to the small sample size. Cognitive impairment decreases patient quality of life.²² Cognitive sequelae showed improvement during follow-up with adequate management and patients' therapeutic control; therefore, it is of the utmost importance for diagnosis to be established in a timely manner and to initiate, to the extent possible, an effective treatment and ensure therapeutic adherence in order to prevent complications.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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