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MA Valle-Murillo¹, ME
Amparo-Carrillo²

¹Department of Neurology and
Psychiatry. National Institute of
Medical Science and Nutrition
"Salvador Zubiran."

²Mexican Social Security Institute,
Family Medicine Unit #58

Central nervous system infections, part 2: Neuroinfections in patients with human immunodeficiency virus infection

Infecciones del Sistema Nervioso Central, parte 2: Neuroinfecciones
en pacientes con Infección por Virus de Inmunodeficiencia Humana

Abstract

Since the first reports of Human Immunodeficiency Virus (HIV) infection, the field of infectology has changed in a vertiginous way resulting in the appearance of two new subspecialties: HIV infectology and neuroHIV—the latter focused in the nervous system complications caused by the virus or its treatment.

About 50-70% of patients with HIV infection have or will develop a symptom or neurologic syndrome at some point during the course of their illness, either caused by the virus, an opportunistic infection, or as a complication of the drugs. Among the most common Neurological issues are peripheric neuropathies, neuropsychiatric manifestations, and aseptic meningitis. However, the most challenging and complex aspect by far is the approach to the patient with a suspected neuroinfection in the context of HIV infection, because the immune system has been compromised and its response might not be the one expected in an immunocompetent patient. That's why a special algorithm must be designed for the diagnosis and management of this population.

Keywords

Neuroinfections, meningitis, hiv, toxoplasma encephalitis, cryptococcal meningitis.

Resumen

Desde la aparición de los primeros casos con infección por el virus de inmunodeficiencia humana (VIH) la infectología se ha revolucionado de una forma vertiginosa de tal forma que actualmente existen subespecialidades dentro de la infectología que se dedican al estudio de pacientes con VIH y dentro de la neurología que se enfocan en las complicaciones en el sistema nervioso causadas por el virus o su tratamiento.

Se estima que entre el 50-70% de los pacientes con infección por VIH tienen o tendrán en algún momento un síntoma o síndrome neurológico ya sea causado directamente por el virus, por un oportunismo o como complicación del tratamiento. Dentro de las complicaciones más comunes se encuentran las neuropatías periféricas, cambios neuropsiquiátricos y la meningitis aséptica, sin embargo definitivamente el aspecto más complejo es el abordaje de un paciente con sospecha de neuroinfección en el contexto de VIH ya que el sistema inmunológico se encuentra alterado y la respuesta puede no ser la misma que en el caso de una persona inmunocompetente por lo que se requiere de un algoritmo especial para el diagnóstico y manejo de esta población.

Palabras clave

Neuroinfecciones, vih, meningitis, toxoplasmosis, criptococosis.

Corresponding Author:

Dr. Miguel Angel Valle Murillo. Vasco de Quiroga 15,
Colonia Belisario Domínguez Sección XVI, Tlalpan C.P.14080,
Ciudad de México, D.F.
E-mail: mvalle.md@gmail.com

Introduction

Facing a neurological case in the context of a patient living with HIV is very particular and requires all the skills and knowledge of the internist, infectious disease specialist, or neurologist managing the case. We know the immune response is compromised and therefore some manifestations derived from it such as fever, pleocytosis, hyperproteinorraquia, or intracranial hypertension may be barely present or not found at all. In these cases, it is of vital importance to consider the CD4+ cell count as well as the use of antiretroviral drugs and chemoprophylaxis for opportunism. We can also find the case of a patient with a high CD4+ count who is on antiretrovirals, presenting with a rare picture of neuroinfection which may be due to immune reconstitution or the rare syndrome of viral escape in cerebrospinal fluid (CSF).¹

Neuroinfections in the patient with HIV infection

The neurology of patients with HIV infection has currently grown in importance since it is known that more than 50% of them have a neurological syndrome either due to the virus itself, which is neurotropic, or opportunism due to immunosuppression or derived from the antiretroviral treatment. This topic is very extensive and, in this section, only the infectious neurological syndromes derived from opportunism in HIV patients will be addressed.¹

I.- Approach to the patient with suspected neuroinfection in hiv

As we mentioned in the first part of this series on neuroinfections, a classification by clinical syndromes is very useful because it allows us to reduce the diagnostic possibilities and we can follow a diagnostic and therapeutic algorithm focused on the most probable cause. Unlike an immunocompetent patient, in the case of a patient with HIV, in addition to considering the predominant clinical presentation, we need to also take into account the CD4 cell count, the adherence to antiretrovirals if they are taken, the use of prophylaxis, and specific risk factors such as visit to caves, consumption of undercooked foods, etc.^{1,2}

Table 1 describes the characteristics of the CSF cytochemistry in the different entities of infectious processes without clinical focalization.

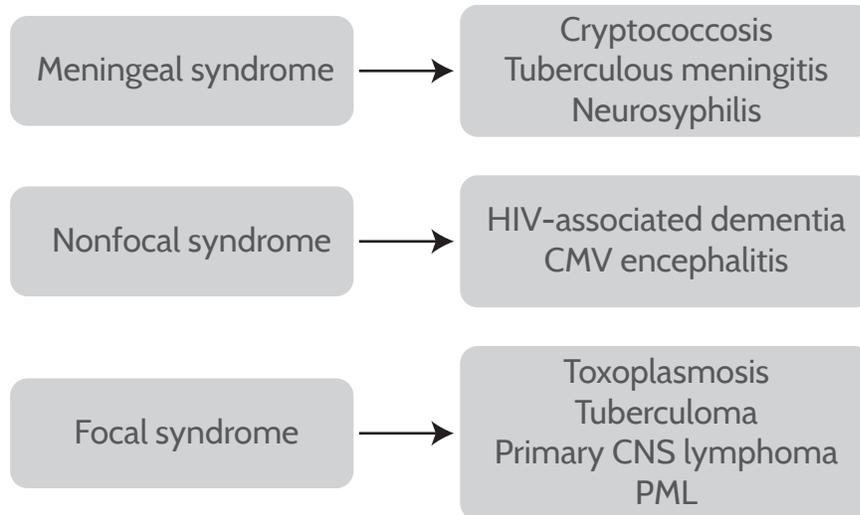
The meningeal syndrome, as already described, is mainly accompanied by meningism, Kerning's sign, and Brudzinski's signs. The non-focal syndrome includes diffuse symptoms such as encephalopathy syndrome, gait disorder, etc. The focal syndrome includes sensory-motor deficits, dysphasia, etc. **Figure 1** describes the causes to be considered depending on the clinical syndrome that predominates. In the case of patients with HIV and encephalopathy syndrome with or without focal symptoms, it is essential to obtain CSF for cultures and special studies depending on the case, without forgetting that HIV infection is an absolute indication to perform neuroimaging

Tablet 1. CSF profile in different entities.

	Leuko (cells)	PMN (%)	Proteins (mg/dL)	Glucose	Opening pressure cm/H ₂ O
ABM	100-10,000	>80	100-500	<10	NI o >20
AM	5-1,000	<60	50-250	10-45	NI
AE	5-100	<60	5-100	10-45	NI
TBM	25-1000	<60	50-1500	10-45	NI o >20

The findings of the analysis of cerebrospinal fluid (CSF) in the main neuroinfections are shown. ABM = acute bacterial meningitis. AM = aseptic meningitis. AE = acute encephalitis. TBM = tuberculous meningitis.

Figure 1. A neuroinfection approach and its differential diagnosis depending on the clinical syndrome in a patient with HIV infection. HIV = human immunodeficiency virus. CMV = cytomegalovirus. CNS = central nervous system. PML = progressive multifocal leukoencephalopathy.



prior to performing a lumbar puncture (LP) independently of the CD4 count.³

The CSF cytochemistry is usually very similar to that of immunocompetent patients but we must always consider that the inflammatory response may be lower. Although the possibility of neuroinfection due to opportunism must always be kept in mind, the possibility of acute bacterial meningitis (ABM) should not be ruled out, so empirical management for ABM is recommended unless there is a very clear cause from the beginning—for example, in the case of a patient with hemiparesis and neuroimaging compatible with toxoplasmic encephalitis, coverage for ABM would not be necessary in the absence of meningeal syndrome. Whenever a LP is performed in this context, CSF cultures should be requested for aerobic bacteria, anaerobes, mycobacteria, bacterial antigens, India ink stain, cryptococcal antigen, venereal disease research laboratory (VDRL) and protein chain reaction (PCR) for herpes simplex virus (HSV), varicella zoster, and cytomegalovirus (CMV). In blood, VDRL, toxoplasma IgG, and blood culture should be requested.³

The next step in the diagnostic-therapeutic

approach is neuroimaging either by tomography or cranial magnetic resonance imaging. This way, we can divide it into four radiological presentations.

* **Group 1:** Normal image or with diffuse meningeal enhancement suggests bacterial or fungal meningitis as first possibilities and MTB or neurosyphilis as second options. For this group, request bacterial cultures, mycobacteria, cryptococcal antigen, adenosine deaminase (ADA) and VDRL. Empirical treatment should include antibiotic for ABM and consider amphotericin B in case of cryptococcal antigen and anti-tuberculosis drugs in case of ADA > 10.

* **Group 2:** Basal enhancement. There may be multiple differential diagnoses but, in this context, the main suspect is tuberculous meningitis (TBM) so an ADA > 10 or some other finding compatible with TBM suggests initiation of anti-tuberculosis drugs.

* **Group 3:** focal lesion either in basal or subcortical gray nuclei. Stronger alternatives such as toxoplasmosis should be considered, especially if there is ring enhancement. For its approach, serotype IgG for toxoplasmosis is recommended and consider a brain SPECT (Single

Photon Emission Computed Tomography). The therapeutic approach, in this case, is to start treatment for toxoplasmic encephalitis even if the toxoplasmosis IgG is negative. If it fails, then treat as possible lymphoma.

***Group 4.** Diffuse lesions in white matter. They comprise many etiologies, but the more important are progressive multifocal leukoencephalopathy (PML) and HSV or HIV encephalitis. The diagnostic approach in this group should include CSF with bacterial cultures, HSV PCR, VZV, CMV, and JC virus. Acyclovir can be initiated empirically if the clinic suggests viral encephalitis, pending the results of other studies. See [Table 2](#).⁴

The most important infectious syndromes are briefly discussed below.

II.- Bacterial meningitis

This topic was already addressed in the previous article, but we must emphasize the fact that in the context of HIV the meningeal signs are absent and suspicion should remain high in case of headache and fever without clear explanation. The CSF is usually very similar to that of its immunocompetent counterpart. The etiologies are usually the same although *L. monocytogenes* is slightly more prevalent in this group of patients, so empirical coverage is recommended for it. The

empirical treatment is the same as described in [Figure 4](#).⁵

III. Central nervous system tuberculosis

This topic will be discussed in more detail in a special section; however, it is important to mention in this article because the risk of tuberculosis in HIV is 1 in 3. Twenty percent of all cases are associated with HIV and it's currently the most common cause of death in the AIDS population.⁶ The most common form of infection in the CNS is TBM. TBM can occur simultaneously with the primary infection, which happens mainly in children, but in adults it is usually due to reactivation of a previous infection. Transmission is through the inhalation of drops. During primary infection, it germinates in the brain, spinal cord, and meninges forming the "Rich focus" which can break into the subarachnoid space where it produces inflammatory exudates that favor the development of meningitis.^{6,7}

Clinically, in an immunocompetent patient, it presents with a prodrome. Like many neuroinfections, it is accompanied by nonspecific symptoms such as fever, headache, malaise, and nausea. Unlike bacterial meningitis, which is characterized by an acute picture of days of evolution, TBM presents as a subacute or chronic meningitis that develops over a period of two to eight weeks.^{6,7}

Table 2. Approach to neuroinfection in HIV by neuroimaging.

Group 1	Normal image or diffuse meningeal enhancement	Bacterial meningitis, meningeal cryptococcosis, meningeal tuberculosis, neurosyphilis
Group 2	Basal level enhancement	Tuberculous meningitis
Group 3	Focal lesion with edema in the basal or subcortical gray nuclei	Toxoplasma encephalitis, primary CNS lymphoma
Group 4	Diffuse lesions in white matter	PML, HIV encephalitis, HHV-6 or CMV encephalitis, infectious vasculopathy

Depending on the neuroimaging findings, the picture of a neuroinfection in a patient with HIV can be divided into four groups and this reduces the differential diagnoses as shown in the table. CNS = central nervous system. PML = progressive multifocal leukoencephalopathy. HIV = human immunodeficiency virus. HHV = human herpesvirus. CMV = cytomegalovirus.

The clinical presentation in the patient with HIV is very similar, but the alteration of the early warning state is more prevalent. The CSF is reported with little cellularity and predominance of mononuclear cells. Microscopy has a very variable sensitivity of 25-50% but increases up to 80% with large samples 20ml and repeated. The culture has 50% sensitivity. Currently, the preferred technique for detection of TB in CSF is GeneXpert—with a sensitivity of 80% and specificity of 97%, it is positioning itself as the preferred diagnostic method from the start.^{8,9}

By image, meningeal enhancement is usually observed at the basal level delimiting the arteries of the circle of Willis, although less intense than in the immunocompetent, and there may be hydrocephalus which progresses insidiously. **Figure 2.** Mortality at 6-9 months is 24-60% vs 0-30% of the immunocompetent.⁶

The treatment in all forms of TB requires a combination of the four classic anti-tuberculosis drugs: rifampicin, isoniazid, pyrazinamide, and ethambutol. The addition of pyridoxine to avoid toxicity is very important. In addition, it should be considered that the prevalence of multidrug resistance is greater (13-40%) than that of the immunocompetent (2-5%) and taking into account that the penetration of anti-tuberculosis drugs to the CNS could be poor, it is suggested to consider the addition of secondary anti-tuberculosis drugs. There are some complications observed mainly in the patient with HIV, such as a decrease in the plasmatic levels of rifamycin by HIV itself or by drug interaction. Immune reconstitution inflammatory syndrome (IRIS) in two forms: 1) IRIS with TBM unmasked - new diagnosis of TBM in patient without previous TB; 2) paradoxical IRIS - new signs of TBM, tuberculoma or complications due to TBM in a patient with a previous diagnosis of TBM.^{6,7}

IV.- Cns cryptococcosis

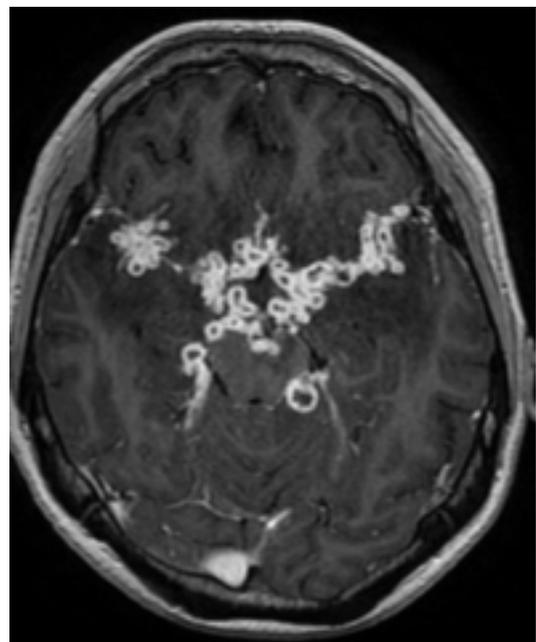
An infection by *Cryptococcus neoformans*, an encapsulated yeast transmitted via respiratory airways, is the most common fungal infection in

patients with HIV. It usually occurs with <100 CD4.¹⁰

The most common presentation is meningeal cryptococcosis. It presents as subacute-chronic meningitis with insidious onset, fever, headache, nausea, vomiting, and cognitive deterioration followed by an altered state of alertness. Ophthalmoparesis, alterations in the visual field, and papilledema are frequent findings in the neurological examination due to the subacute intracranial hypertension they develop.¹⁰

Meningeal syndrome might be found, though it's often absent in the context of HIV. In the suspicion of meningeal cryptococcosis, it is recommended to obtain neuroimaging, as indicated in all HIV patients with neuroinfection, before performing a LP. The cytochemistry is similar to that found in viral encephalitis or aseptic meningitis. India ink is reported in a few hours and can be useful for an early start of treatment, but its sensitivity is low <50%. The opening pressure is usually high.

Figure 2. Magnetic resonance imaging of a case of tuberculous meningitis. A basal arachnoiditis is observed, affecting most of the circle of Willis.



The antigen in CSF has a sensitivity of 91% and a specificity of 95%.¹⁰

The definitive diagnosis is made by CSF culture, which has a sensitivity of 70-95%. The tomography and MR are usually normal, occasionally showing meningeal enhancement and pseudocystic lesions in deep perivascular spaces such as the territory of lenticulostriate or cryptococcoma.^{10,11}

The management recommended by IDSA guidelines is amphotericin B 0.7mg-1mg/kg/day + flucytosine 100mg/kg/day; however, in Mexico, the latter is not available, so fluconazole 800mg per day is used as an alternative. The induction therapy described must be continued for at least two weeks. If the induction therapy was satisfactory (defined as clinical improvement and negative CSF culture), consolidation can be initiated and, finally, maintenance therapy. It is important to consider that the CSF cytochemistry in cases of meningeal cryptococcus may have minor changes after the induction phase, so it should NOT be considered a treatment failure if the cell count, protein, or glucose ratio does not change significantly since this can happen in most chronic meningitis.^{10,11}

In case of intracranial pressure >25cm H₂O it is recommended to decrease the pressure through draining liquids by 50% or else 20-30 ml. The measurement and drainage must be done—every day, if necessary—until it is normal. Steroids or acetazolamide are not useful in these cases. If the punctures need to be frequent, external lumbar drainage can be done and, in select cases, surgical drainage.¹⁰

Because intracranial hypertension develops chronically, the patients, despite having papilledema and ophthalmological alterations, do not usually show signs of instability if they receive treatment.^{10,11}

V.- Toxoplasmic encephalitis

Toxoplasmic encephalitis (TE) is the inflammation of the cerebral parenchyma secondary to infection by *T. gondii*. It is the most common cause of focal brain syndrome in a patient with HIV. The prevalence of *T. gondii* infection in Latin America reaches 70%. It may present as cerebritis, abscess, diffuse encephalitis and usually appears with CD4<100 cells. Due to reactivation of previous exposure, the clinical picture is established insidiously and progressively in the course of weeks to months. About 50% have fever and headache, and TE has tropism for gray nuclei, so movement disorders—mainly focal chorea and ballism—are not rare. **Table 3.**^{10,11}

Diagnosis is usually relatively simple since the picture is typical: patient with HIV—or suspicion of it due to risk factors—without antiretrovirals, presents with a neurological focal syndrome, plus frequent hemiparesis and dysphasia. Imaging finds multiple lesions (60-70%), hypodense on CT, hypointense on T1, iso- or hypointense on T2, with gadolinium ring enhancement, and localization at the supratentorial gray nuclei, thalamus, and corticomedullary junction. **Figure 3.**^{10,11,12}

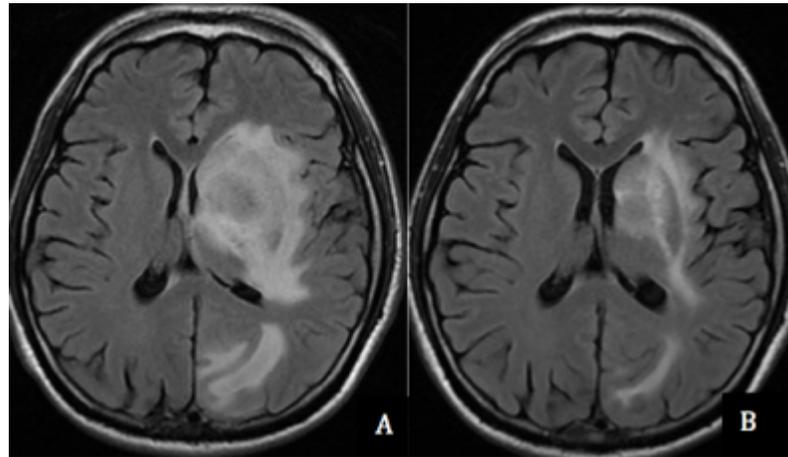
The serology for toxoplasma IgG is present in >90% of the cases and its absence must force a reconsideration of the diagnosis; however, it is

Table 3. Signs and symptoms of toxoplasmic encephalitis.

Sign/symptom	Frequency %
Subcortical or cerebellar - gait disorder	51%
Focal-cortical - monoparesis/hemiparesis	65%
Focal-cortical - dysphasia/aphasia	55%
Diffuse - headache	61%

The frequency of the signs and symptoms of toxoplasmic encephalitis is shown depending on the tomography of the lesion.

Figure 3. Magnetic resonance imaging of a case of toxoplasmic encephalitis. The left side (A) is prior to treatment and the right side (B) after treatment.



not used as diagnostic method, only suggestive of it. The definitive diagnosis is made by biopsy but it is rarely considered if there is no treatment failure. The most important differential diagnosis is with primary central nervous system lymphoma (PCNSL) which presents in a very similar way, both clinically and by imaging. In case of focal lesion with edema, it is always handled initially as TE and if the treatment fails then it is approached as PCNSL. If, however, from the beginning there is data suggestive of PCNSL or serology absent for *T. gondii*, then an early SPECT is recommended. The SPECT is performed with thallium 201, comparing the lesion against a healthy hemisphere or uptake ratio. The increase in uptake is compatible with lymphoma. In TE cases there is no increase—there might even be a decrease in uptake. Its sensitivity is 92% and specificity 89%, though lesions <1cm or with necrotic areas interfere with sensitivity.^{10,11,12}

* Management: it was already mentioned that any focal lesion with edema should be treated as TE. The treatment recommended by the IDSA and the DHHS guidelines for opportunistic management is pyrimethamine with a loading dose of 100-200mg and then 75-100 mg a day, always accompanied by folic acid + sulfadiazine 6-8 gr a day or clindamycin IV 900 mg every six hours for at least six weeks.

Steroids: the use of steroids deserves special mention because its administration is often abused with TE. The indication for steroids use is only in

case of significant mass effect that conditions imminent herniation or important neurological deterioration; otherwise, it is recommended to avoid or discontinue their use as soon as possible since they do not allow an objective evaluation of the response to treatment. The recommendation is dexamethasone 4-8 mg IV every 6 hours.^{10,12}

To interpret the response to treatment, a scale has been proposed where the clinical manifestations are graded by category. [Table 4.](#)^{12,13,14}

Neurological response is defined as improvement of at least 50% in at least one clinical category, without worsening in some other category, and without the appearance of new symptoms in another category. The neurological response occurs in 50% at three days, 86% at day seven, and 90% at 14 days. At seven days, 70% of the cases had at least 50% improvement. The cut to evaluate response is at 14 days, and the scale must be repeated.¹⁴

The imaging response is divided into categories: Complete: study of image without injuries; Good: decrease of >50% of the lesions, without new lesions or worsening of others; Partial: decrease of <50% of a lesion, without increase in size or appearance of new lesions; Mixed: any decrease in size with increase or appearance of others.¹⁴

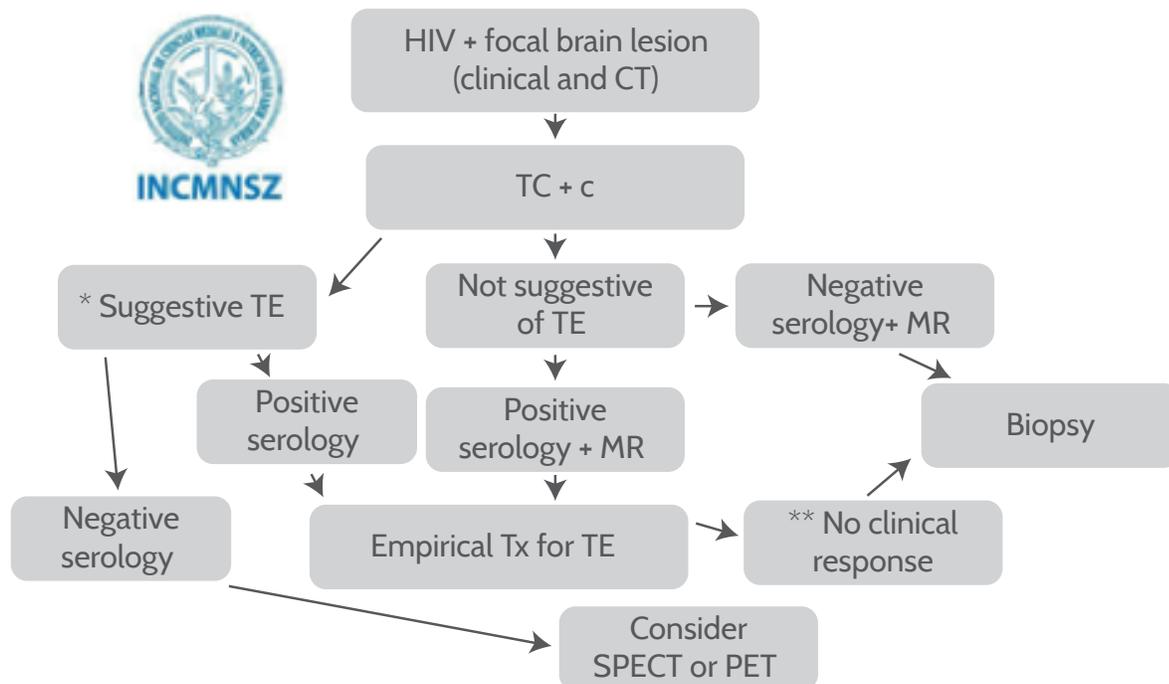
Table 4. Systems to be evaluated in the clinical evolution of CNS toxoplasmosis.

Category	Sign/symptom
Diffuse cortical or multifocal	Alertness, memory, evocation, and orientation.
No locator	Headache, seizures.
Subcortical or cerebellar	Balance, gait, sensitive, chorea.
Focal cortical	Visual fields, language, language fluency, comprehension, repetition, MT force, MP force, global force.
Infratentorial	Facial paralysis, diplopia, ophthalmoparesis, sphincter control.

For clinical follow-up and to determine the response to treatment in toxoplasmic encephalitis, the clinical categories shown in the table should be evaluated. CNS = central nervous system.

Figure 4. Algorithm for management of a patient with HIV and focal brain injury.

HIV = human immunodeficiency virus. CT = computed tomography. TC + c = contrast tomography. TE = toxoplasmic encephalitis. MR = magnetic resonance. SPECT = single-photon emission computed tomography. PET = positron emission tomography.



* Multiple lesions less than 3cm, with ring enhancement, in basal ganglia, thalamus, or corticomedullary junction.

** Improvement >50% in at least one clinical category without worsening or appearance of lesions in other categories.

Conclusions

The approach to the patient with an infection in the central nervous system requires a multidisciplinary team and it is important to always consider there are no rigid protocols because the clinical presentations can be very variable. Initially, therapeutics should be guided by the characteristics of the patient such as age, gender, co-morbidities, immunosuppression status, and risk factors such as travel, immunizations, previous use of antibiotics, etc. The rapid establishment of adequate therapy offers the opportunity for a good outcome with little or no long-term disability as well as a lower rate of morbidity and mortality.

Conflicts of interest

There are no potential conflicts of interest for any of the authors in this scientific report.

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References

1. Corral I, Quereda, Carmen. The Neurological spectrum of HIV infection. In: García.Moncó JC. CNS Infections, a clinical approach. Vizcaya, España. *Springer*. 2014:229-239
2. Verma A, Berger J. Neurological manifestations of Human Immunodeficiency virus infection. In: Daroff R. Bradley's Neurology in clinical practice. Philadelphia. *Elsevier*. 2012: 1211-1230
3. Marra C. Infections of the central nervous system in patients with human immunodeficiency virus. *Continuum*. 2006.
4. Tan I, Smith B, von Geldern G, Mateen F, McArthur J. HIV-associated opportunistic infections of the CNS. *Lancet Neurol*. 2012; 11: 605-17
5. Fitch M, van de Beek D. Emergency diagnosis and treatment of adult meningitis. *Lancet Infect Dis*. 2007;7:191-200.
6. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British infection society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *Journal of infection*. 2009. 59,167-187.
7. Thwaites G, Hien T. Tuberculous meningitis: many questions, too few answers. *Lancet Neurol*. 2005; 4;:160-70
8. Berenguer J, Moreno S, Laguna F, Vicente T, Adrados M, Ortega A *et al*. Tuberculos meningitis in patients infected with the human immunodeficiency virus. *Nejm*. 1992. 326: 10; 668-672-
9. Dekinger C, Schumacher S, Boehme C, Dendukuri N, Madhukar P, Steingart K *et al*. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *Euro Resp J*. 2014: 44; 435-446.
10. Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents:Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014 May;58(9):1308-11
11. Avindra N. Neurologic complications of human immunodeficiency virus infection. *Continuum*. (Minneap Minn) 2015; 21: 1557-1576.
12. Berger J. Pearls: Neurologic complications of HIV/AIDS. *Semin Neurol*. 2010. 30 (1) 66-70.
13. Soto J. Toxoplasmosis cerebral en pacientes con infección por VIH-SIDA. *Enf Infec y Microbiol*. 199; 19:10-7.
14. Luft B, Hafner R, Korzun A, Leport C, Antoniskis D, Bosler E z. Toxoplasmosis encefalitis in patients with the acquired immunodeficiency syndrome. *Nejm*. 1993. 329; 14: 995-1000

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