Features to validate cerebral toxoplasmosis

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ABSTRACT

Introduction: Neurotoxoplasmosis (NT) sometimes manifests unusual characteristics. Methods: We analyzed 85 patients with NT and AIDS according to clinical, cerebrospinal fluid, cranial magnetic resonance, and polymerase chain reaction (PCR) characteristics. Results: In 8.5%, focal neurological deficits were absent and 16.4% had single cerebral lesions. Increased sensitivity of PCR for Toxoplasma gondii DNA in the central nervous system was associated with pleocytosis and presence of >4 encephalic lesions. Conclusions: Patients with NT may present without focal neurological deficit and NT may occur with presence of a single cerebral lesion. Greater numbers of lesions and greater cellularity in cerebrospinal fluid improve the sensitivity of PCR to T gondii.

Keywords: AIDS. Cerebral toxoplasmosis. Diagnosis.

Neurotoxoplasmosis (NT) is the most frequent opportunistic infection of the central nervous system (CNS) among individuals with the acquired immunodeficiency syndrome (AIDS). It indicates severe immunodeficiency and, if it remains untreated, it may lead to death.

The number of cases of NT in Brazil and around the world has declined since 1996, the year highly active antiretroviral therapy (HAART) was introduced. Nonetheless, it is still the most common opportunistic infection of the CNS in Brazil and the third most common AIDS-defining disease in São Paulo.

In countries with a high seroprevalence of toxoplasmosis, the incidence of NT has been estimated to be between 30% and 40% among AIDS patients who are not receiving prophylaxis. Even though NT is frequent neurological manifestation, pleomorphic presentations of the infection are not uncommon, and differential diagnoses must include other neurological infections and tumor diseases.

The aim of the present study was to describe important features of NT that might contribute to recognition of the disease, thereby avoiding delayed diagnoses. The descriptive cross-sectional study was conducted between February 2006 and December 2008, at 2 referral centers for neurological diseases in the City of Recife, State of Pernambuco, Brazil, the Hospital da Restauração and the Oswaldo Cruz University Hospital.

Eighty-five AIDS patients were included in the study. They all also had a diagnosis of NT that had been determined using the criteria of the Centers for Disease Control and Prevention (CDC). These criteria include: I) presence of a recent neurological abnormality consistent with intracranial disease; II) evidence of a cerebral lesion with a mass effect viewed using cranial tomography or magnetic resonance imaging (MRI); III) positive serological findings of Toxoplasma gondii; and IV) a therapeutic response to toxoplasmosis treatment. Aliquots of cerebrospinal fluid (CSF) were subjected to real-time and PCR analysis for detection of the b1 gene of T. gondii.

The patients were characterized by variables relating to gender, age, and presence of focal neurological deficits.

We defined the therapeutic response as good in cases in which there was a clinical and radiologic improvement with regression of neurological signs and symptoms following institution of therapy, which consisted of sulfadiazine in association with pyrimethamine or clindamycin, both administered together with folinic acid.

Patient follow up was maintained for an average of 90 days. This study was approved by the Research Ethics Committee for studies involving human beings, and was given the protocol number 00430.102.172/05.

There were 43 men and 42 women evaluated, with a mean age of 35.8 ± 0.98 years. The time for neurological symptoms to become established ranged from 1 to 90 days, with a median of 14 days. At the time of diagnosis of cerebral toxoplasmosis, 65.8% of the patients were known to have been HIV-positive.

Among the most frequent manifestations, we observed hemiparesis in 75 (88.2%) cases, headache in 76 (89.4%), and fever in 46 (54.1%).

Thirty-nine (45.9%) patients presented with convulsive crises. Analysis of the presence of seizures in patients with up to 4 encephalic lesions in relation to a group with more than 4 lesions did not show any statistically significant difference (p = 0.89). However, analysis of whether the seizures depended
on lesion location showed that patients with cortical lesions had a greater rate of seizures than did a group with deep lesions, and this difference was statistically significant (p = 0.02).

Ten (8.5%) patients did not present with any focal neurological signs, and among this group, the initial manifestation consisted predominantly of onset of convulsive crisis.

With regard to level of consciousness, 71 (83.5%) patients were alert. However, among this group, 47% presented with states of confusion on admission to hospital.

Deficits of cranial nerve pairs were observed in 12 (14.1%) patients, with CN III most (66.6%) frequently affected.

CD4 evaluations revealed a mean count of 66.6 cells/mm³, with 93%-94% of the cases serologically positive for anti-Toxoplasma IgG.

Eighty-three samples of cerebrospinal fluid were evaluated, and pleocytosis was observed in 52 (62.6%) cases, with a mean cell density of 27.1 cells/mm³. The predominant pattern was lymphomononuclear. High levels of cerebrospinal fluid proteins were also present in 85.3% of the cases, with a mean protein concentration of 104.4mg/dL.

Cranial magnetic resonance imaging (MRI) was performed in 69 cases. Cases with 4 or more encephalic lesions predominated, accounting for 55.1% of all cases. There were 14 (16.4%) patients with single cerebral lesions (Figures 1 and 2).

On analysis of results of real-time PCR seeking T. gondii DNA in the CSF, with regard to cell density in the fluid, 89.7% of samples with more than 4 cells/mm³ also had positive PCR results, whereas 35.8% of specimens with up to 3 cells/mm³ had negative PCR results. This difference was statistically significant (p = 0.013).

Analysis of the CSF PCR results in relation to the number of encephalic lesions (as identified by MRI) showed that 54.3% of patients with a maximum of 3 lesions had negative PCR, whereas 73.9% of the group with 4 or more intracranial lesions had positive results from PCR. This difference was also statistically significant (p = 0.026) (Table 1).

Clinical reassessments of 78 patients were performed, and 64 (82.1%) had improvement defined as full regression or recovery from the signs and symptoms. There were 8 (10.3%) deaths, and the PCR results from the cerebrospinal fluid were positive in all 8 cases. Necropsies were only performed in 2 of these cases, and parasitic pseudocysts of T. gondii were observed in both. It was not possible to obtain data on the evolution of the other cases.

With regard to demographic characteristics, we did not find any predominance of the disease according to gender. Some studies have indicated that NT occurs predominantly among males5,6, but without demonstrating statistical significance for such an association7,8. The mean age of patients in our study was similar to that of other studies1,6.

The clinical characteristics most frequently found in our study were hemiparesis, headache, and fever. Subacute forms of presentation were mostly observed. Similar characteristics

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**TABLE 1** - Cellularity of cerebrospinal fluid and number of encephalic lesions with PCR results from cerebrospinal fluid.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCR in cerebrospinal fluid</th>
<th></th>
<th></th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive (n = 29)</td>
<td>negative (n = 53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellularity of CSF (cells/mm³)</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>&lt;4</td>
<td>3</td>
<td>10.3</td>
<td>19</td>
<td>35.8</td>
</tr>
<tr>
<td>≥4</td>
<td>26</td>
<td>89.7</td>
<td>34</td>
<td>64.2</td>
</tr>
<tr>
<td>Lesions seen MRI (n)</td>
<td>(n = 23)</td>
<td>(n = 46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>6</td>
<td>26.1</td>
<td>25</td>
<td>54.3</td>
</tr>
<tr>
<td>≥4</td>
<td>17</td>
<td>73.9</td>
<td>21</td>
<td>45.7</td>
</tr>
</tbody>
</table>

PCR: polymerase chain reaction; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; χ² test; p=0.05 (α=5%).

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FIGURE 1 - Mesencephalic lesion with a central target. (A) and (B), sequences before treatment; (C) and (D), sequences after treatment. Note reduction of the lesion and the cerebral edema. Images: author’s photos.
immunosuppressed individuals serves as an indicator of chronic infection by the parasite, but it does not help to define active disease\textsuperscript{13}. Studies that have evaluated intrathecal synthesis of IgG have shown low sensitivity and consequently little clinical utility\textsuperscript{13,14}. In routine cerebrospinal fluid analysis, findings of moderate pleocytosis with elevated protein concentrations are nonspecific\textsuperscript{13}, but increased cell counts may contribute to greater sensitivity of PCR results, as we found in a previous study\textsuperscript{15} in which we reported on clinical variables that influenced and thereby improved the performance of the method.

The present study showed that single lesions on MRI were not uncommon in individuals with NT (16.4%). However, this finding has yet to be extensively explored with regard to its significance as a diagnostic clue.

In conclusion, additional clinical and imaging variables, especially alongside results from real-time PCR, must be identified to improve the diagnosis of cerebral toxoplasmosis.

\textbf{CONFLICT OF INTEREST}

The authors declare that there is no conflict of interest.

\textbf{REFERENCES}


\textbf{FIGURE 2} Parietal lesion, next to the meningeal plane. (A) and (B), sequences before treatment; (C) and (D), sequences after treatment. Note complete disappearance of the lesion and edema. Images: author’s photos.

