Encephalitis in primary HIV infection: challenges in diagnosis and treatment
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CASE REPORT

Encephalitis in primary HIV infection: challenges in diagnosis and treatment

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Summary: We report a case of primary HIV encephalitis, which initially presented as acute psychosis. Magnetic resonance imaging of the brain was suggestive of vasculitis and multiple infarctions, whereas a brain biopsy after six weeks of symptoms showed HIV encephalitis with microglial nodules, but no signs of vasculitis. We review previous reported cases and radiological findings in HIV encephalitis and discuss the role of antiretroviral therapy and steroids in its management.

INTRODUCTION

It is estimated that 50–90% of individuals infected with HIV develop fever and non-specific symptoms within a few weeks of acquiring the infection; however, in most cases, the symptoms may not be recognized as caused by HIV and diagnosis is delayed, whereby risk of onward transmission is increased. A wide range of neurological complications can occur these are not uncommon. Here we present a case of encephalitis occurring during primary HIV infection. Brain magnetic resonance imaging (MRI) during the early phase of the disease was suggestive of vasculitis and multiple infarctions, whereas a brain biopsy after six weeks of symptoms showed acute HIV encephalitis but no signs of vasculitis. We review radiological findings in HIV encephalitis and discuss the role of steroids in primary HIV encephalitis.

CASE REPORT

A 37-year-old homosexual man presented with flu-like symptoms; a 4th generation HIV (antigen–antibody) test was positive. HIV-RNA was detected whereas a HIV enzyme-linked immunosorbent assay test was non-reactive. He had tested HIV-antibody negative five months prior to presentation. Full blood count and biochemistry were within normal limits and syphilis serology was negative. The patient was offered combination antiretroviral therapy (cART), which he declined due to fear of side-effects. Five days later he was admitted because of a sudden change in behaviour, restlessness, confusion, loss of memory and psychotic symptoms. His temperature was 37.5°C and there was abnormal plantar response and spasticity; the remainder of physical exam was unremarkable. Results of analyses of cerebrospinal fluid (CSF) are summarized in Table 1. Electroencephalography was diffusely abnormal, but without any paroxysm or epileptiform activity. A computed tomography (CT) scan of the brain did not show any abnormalities, whereas MRI with fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI) sequences and angiography revealed multiple small infarctions and enhanced signals of the leptomeninges and perivascularly, especially in the thalamus, suggestive of small vessel vasculitis, but there was no narrowing of the arteries (Figure 1). He was treated with tenofovir, emtricitabine, atazanavir/ritonavir and acyclovir. Due to these findings, pulsed therapy of methyl prednisolone followed by high-dose oral prednisolone was added. Over the following weeks the patient had slight cognitive improvement, but he had spasticity of the lower limbs and the left arm and was unable to stand or walk without support. Repeated MRI showed regression of the perivascular and leptomeningeal signal changes. Six weeks after admission a stereotactic brain biopsy of grey and white substance was performed, which showed classical findings of HIV encephalitis with microglial nodules with rod-shaped cells, ramified cytoplasm and scattered T-cells. (Stains: H&E, van Gieson, Alcian blue, Congo red, MSB, CD3, CD20, CD68, NF, toxoplasmosis, CMV, Herpes, CD34, Ziehl-Nielsen, Grocott.) Stains for other viruses, mycobacteria, fungi and toxoplasmosis were negative. There were no findings suggestive of vasculitis or infarction. After receiving the histological diagnosis, the dose of prednisolone was quickly tapered. During the following weeks the patient improved significantly in both cognitive and motor function. Four months after admission he was neurologically intact but suffered from restlessness, impaired concentration and was diagnosed with bipolar mood disorder by the attending psychiatrist. After one year the patient was doing well without psychiatric illness or cognitive impairment. Viral load was below detection limit and the CD4 cell count was 950 cells/µL.

DISCUSSION

HIV invades the central nervous system (CNS) during acute infection, and HIV-RNA can be found in CSF as early as eight days after transmission. Inflammation is also detectable during acute infection by soluble markers in CSF and through MR spectroscopy. Early invasion of simian immunodeficiency virus in brain tissue of macaques has been demonstrated in an experimental model two weeks after inoculation with the virus. Monocyte-derived macrophages and microglia are the main cell
types infected by HIV, but other cell types such as astrocytes and endothelial cells also contain HIV protein and DNA. HIV infection in the CNS can manifest as meningitis, encephalitis, leucoencephalopathy or vasculitis, and the mechanism of HIV-associated vasculitis involves either direct viral invasion of the vessel wall or immune complex deposition. Clinical neurological manifestations can develop both during acute and chronic infection, in the latter case often in association with severe immunosuppression or treatment interruptions.

Findings of MRI in HIV encephalitis include symmetric, periventricular or diffuse white matter changes. T2WI and FLAIR show focal abnormalities of high signal intensity. Lesions are typically located periventricularly, in the basal ganglia, cerebellum or brain stem and there may also be atrophy. Table 2 summarizes findings of brain imaging in previous reported cases of acute HIV encephalitis and HIV encephalopathy with no uniform pattern and lesions in both grey and white matter and meninges. CT scans detected abnormalities in only three of 20 cases, all three were fatal; whereas MRI was abnormal in 11 of 21 cases, two of which were fatal. In the present case MRI was suggestive of vasculitis and prompted treatment with high-dose prednisolone. MRI with FLAIR and DWI sequences is considered to have an excellent sensitivity for detecting cerebral vasculitis of different aetiologies, but with much lower specificity. Brain biopsy is required for a definite diagnosis of cerebral vasculitis. The sensitivity of biopsy has been reported as low as 75%, due to sampling error, which can be reduced by performing the biopsy stereotactically. In the present case, MRI findings were not confirmed by a stereotactic brain biopsy, which was performed one month after initiation of prednisolone and showed no evidence of vasculitis. Whether the vasculitis had resolved following treatment or MRI findings were non-specific remains elusive. However, the low level of HIV-RNA in CSF, a relatively high CD4 count, absence of other pathogens being detected despite extensive examinations, the pattern of MRI changes and the response to treatment points towards an exaggerated immune response as an important pathogenic factor in the clinical presentation of this case.

The clinical improvement our patient experienced may be due to cART, prednisolone or reflected the natural course of disease. There are only few case reports of outcomes of treatment with steroids in primary HIV encephalitis (Table 2) and firm conclusions cannot be reached, but there is no indication of a dramatic effect. Whereas steroids have a central role in the management of CNS vasculitis of autoimmune pathogenesis, evidence for the use of steroids in HIV-associated vasculitis or other types of viral encephalitis is lacking, although case reports indicate that steroids may be effective in varicella zoster encephalitis and in viral encephalitis complicated by cerebral oedema.

Individuals with neurological manifestations of primary HIV infection should initiate cART as these manifestations are associated with accelerated progression of HIV. Initiation of cART during primary infection may have long-term benefits by reducing the latent viral reservoir, lowering the viral set point and preserving immune function and can potentially reduce transmission. Although data on the effect of cART in reducing the risk of severe complications of primary HIV infection are lacking, we believe that patients presenting with CNS symptoms as part of a primary infection should be offered...
Table 2: Summary of previous reported cases of encephalitis and encephalopathy associated with primary HIV infection

<table>
<thead>
<tr>
<th>Ref</th>
<th>Gender, age</th>
<th>Duration</th>
<th>cART</th>
<th>Steroids</th>
<th>Outcome</th>
<th>CD4 count (cells/μL)</th>
<th>HIV RNA (copies/mL)</th>
<th>CSF VL (copies/mL)</th>
<th>CSF (10^6 Cells/L)</th>
<th>CSF protein (g/L)</th>
<th>Biopsy</th>
<th>CT</th>
<th>MRI</th>
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<tbody>
<tr>
<td>8</td>
<td>M, 20</td>
<td>5 d</td>
<td>Yes</td>
<td>Yes</td>
<td>Recovered</td>
<td>30</td>
<td>0</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M, 29</td>
<td>4 d</td>
<td></td>
<td></td>
<td>Recovered</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M, 42</td>
<td>4 m</td>
<td>Yes</td>
<td></td>
<td>Fatal</td>
<td>329</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F, 31</td>
<td>5 d</td>
<td>Yes</td>
<td></td>
<td>Fatal</td>
<td>&lt;3</td>
<td>1.1</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td>F, 25</td>
<td>14 d</td>
<td></td>
<td></td>
<td>Recovered</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>13</td>
<td>M, 37</td>
<td>4 d</td>
<td></td>
<td></td>
<td>Fatal</td>
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</tr>
<tr>
<td>14</td>
<td>F, 47</td>
<td>4 d</td>
<td>Yes</td>
<td></td>
<td>Recovered</td>
<td>107</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
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<td></td>
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<tr>
<td>15</td>
<td>M, 26</td>
<td>6 d</td>
<td>Yes</td>
<td></td>
<td>Recovered</td>
<td>140</td>
<td>55</td>
<td>1.8</td>
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<td>Normal</td>
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<tr>
<td>16</td>
<td>M, 33</td>
<td>&gt;16 m</td>
<td>Yes</td>
<td>AZT</td>
<td>Improved</td>
<td>349</td>
<td>2</td>
<td>0.7</td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
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<tr>
<td>17</td>
<td>F, 22</td>
<td>5 m</td>
<td></td>
<td></td>
<td>Fatal</td>
<td>60</td>
<td>46</td>
<td>1.9</td>
<td></td>
<td></td>
<td>Normal</td>
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</tr>
<tr>
<td>18</td>
<td>M, 22</td>
<td>2 w</td>
<td></td>
<td></td>
<td>Recovered</td>
<td>389,000</td>
<td>2</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
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<tr>
<td>19</td>
<td>F, 27</td>
<td>1 m</td>
<td>Yes</td>
<td>Yes</td>
<td>Sequeilae</td>
<td>29,000,000</td>
<td>86,000</td>
<td>512</td>
<td>1.3</td>
<td></td>
<td>Hyperintense lesions in subcortical and periventricular white matter and frontal and temporal lobes grey matter</td>
<td></td>
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</tr>
<tr>
<td>20</td>
<td>M, 34</td>
<td>2 w</td>
<td></td>
<td></td>
<td>Recovered</td>
<td>204</td>
<td>5800</td>
<td>33</td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>M, 31</td>
<td>11 d</td>
<td>Yes</td>
<td></td>
<td>Fatal</td>
<td>621</td>
<td>&gt;50,000</td>
<td>217</td>
<td>1</td>
<td></td>
<td>Ischaemic neuronal damage, widespread necrosis, Mixed perivascular infiltrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>M, 45</td>
<td>5 m</td>
<td>Yes</td>
<td></td>
<td>Improved</td>
<td>690</td>
<td>1,300,000</td>
<td>106,000</td>
<td>0.7</td>
<td></td>
<td>Normal</td>
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<tr>
<td>23</td>
<td>M, 30</td>
<td>2 d</td>
<td>Yes</td>
<td></td>
<td>Recovered</td>
<td>44</td>
<td>550,000</td>
<td>4,840,000</td>
<td>633</td>
<td></td>
<td>High signal intensity of the bilateral globus pallidus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>M, 59</td>
<td>5 d</td>
<td></td>
<td></td>
<td>Recovered</td>
<td>2,900,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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(Continued)
Treatment. The role of steroids in acute HIV encephalitis has not been defined and, in our opinion, steroids should be withheld unless there is strong suspicion of an auto-immune component in the pathogenesis.

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