HIV and CNS
Stereotactic Biopsy in the diagnosis
of brain lesions in AIDS patients

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Definition

✓ AIDS Patients

- Patients with high life risk due to HIV infection

- Associated pathologies or systemic diseases caused by the HIV
Classification of patients infected with HIV-1
Clinical Subgroups

✓ A : Acute infection/ Asymptomatic HIV+ patient
B : Symptomatic patients not included in A or C (oropharyngeal or vulvovaginal candidiasis, cervical dysplasia or in situ carcinoma, peripheric neuropathy, LOV, VHZ, PTI, pelvic inflammation disease)
C : Markers diseases of AIDS
## Classification of patients infected with HIV-1

### Clinical Subgroups

<table>
<thead>
<tr>
<th>CD4 LEVELS</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 500/mm</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
</tr>
<tr>
<td>200-499/mm</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>&lt; 200/mm</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>
Course of Neurologic Disease and HIV Infection in Adults

Clinical latency or mildly symptomatic disease

Acute retroviral

Neuropathic manifestations (headache, retroorbital pain, pain on EOM, photophobia (30%), meningoencephalitis, peripheral neuropathy

HIV aseptic meningitis - any CD4 level

Bacterial meningitis,
(S. pneumoniae, H. influenzae, N. meningitidis)
TB meningitis
CNS Syphilis or Nucleoside toxicity (ddI, ddC, d4T, 3TC)
can occur at any CD4 level

Herpes zoster
Mononeuritis multiplex

Coincidental
(Non HIV-1 associated)
can occur at any CD4 level

AIDS dementia complex
[Coccidioides or Histoplasma meningitis]
[Cryptococcosis Toxoplasmosis]
PML Primary CNS Lymphoma CMV mononeuritis multiplex, encephalitis
Neurologic Symptoms in AIDS

- 50% develop neurologic symptoms
- 10% present initially with neurologic complaint
- 10-20% normal brain on autopsy
Neurological symptoms are very often found in HIV AIDS disease and it usually has a very high morbidity and mortality. It appears in any stage of the disease.
CNS involvement

- First stage or Acute Retroviral Syndrome:
  - aseptic meningitis, seroconversion acute mielitis, peripheral neuropathies, Guillain-Barré S.
- Middle or chronic stage:
  Immune mediated neuropathies, Antiretroviral toxicity
- Final stage or AIDS:
  - CNS infections
  - CNS tumors
CNS infections

| PARASITIC INFECTIONS | • PARASITIC INFECTIONS :
| Toxoplasmosis | Toxoplasmosis |
| Trypanosomiasis | Trypanosomiasis |

| FUNGAL INFECTIONS | • FUNGAL INFECTIONS :
| Criptococcosis | Criptococcosis |
| Candidiasis | Candidiasis |
| Aspergillosis | Aspergillosis |
| Histoplasmosis | Histoplasmosis |

| BACTERIAL INFECTIONS | • BACTERIAL INFECTIONS :
| Tuberculosis | Tuberculosis |
| Micoabacterium a.i. | Micoabacterium a.i. |
| Treponema | Treponema |
| Bacterial infections | Bacterial infections |

| VIRAL INFECTIONS | • VIRAL INFECTIONS :
| CMV | CMV |
| PML/JCV | PML/JCV |
| HSV | HSV |
| VZV | VZV |
CNS tumors

✓ Primary CNS Lymphoma
✓ Secondary Lymphoma
✓ Kaposi Sarcoma
✓ Gliomas ??
Mechanism of action of HIV-1

Direct Mechanism
• HIV infection of cells

Indirect Mechanism
• Toxic effect of HIV-1 proteins over neuronal tissue
• Interaction between glial cells and infected macrophages
• result in neuronal damage
• NMDA receptor associated with neuronal damage

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HIV-CNS-Pathophysiology


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Diagnostic Algorithm

NEUROLOGICAL

CT / MRI

NORMAL

CSF/SEROLOGY

ABNORMAL

ABNORMALITIES/NO

CSF/SEROLOGY

MASS LESION

SINGLE

TOXO TREATMENT?

MULTIPLE

TOXO TREATMENT

NO RESPONSE

RESPONSE

TREATMENT

NEGATIVE

BIOPSY

TREATMENT

BIOPSY

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Stereotactic brain biopsy

- Minimal Invasive Procedure
- Maximal efficacy
- Minimal morbidity
Stereotactic brain biopsy

✓ When?
✓ What for?
✓ How?
✓ Results
Stereotactic brain biopsy

✔ When ?
✔ What for ?
✔ How ?
✔ Results
Stereotactic brain biopsy

- When?
- What for?
- How?
- Results
Stereotactic brain biopsy

- When ?
- What for ?
- How ?
- Results
Stereotactic brain biopsy

- First step: frame
- Second step: image acquisition (CT, MRI).
- Third step: planning.
- Forth step: biopsy
Frame
Image acquisition
Planning
Biopsy
• ¿¿ Is the biopsy representative of the lesion ???
Diagnostic yield

**Intraoperative:**
- sensitivity 78%
- specificity 90%

**Cytology:**
- sensitivity 88%
- specificity 90%
STEREOTACTIC BIOPSY IN AIDS PATIENTS
(N = 300)

- PCNSL
- PML
- TOXO
- CHAGAS
- ENCEPHALITIS
- CRIPTO
- TBC

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STEREOTACTIC BIOPSY IN AIDS PATIENTS (N = 300)
### Diagnosis

**N=300**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNSL</td>
<td>88</td>
<td>29.3%</td>
</tr>
<tr>
<td>PML</td>
<td>69</td>
<td>23%</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>46</td>
<td>15.3%</td>
</tr>
<tr>
<td>Chagas Disease</td>
<td>16</td>
<td>5.3%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>12</td>
<td>4%</td>
</tr>
<tr>
<td>Encephalitis-VIH</td>
<td>12</td>
<td>4%</td>
</tr>
<tr>
<td>Cryptococcoma</td>
<td>8</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASCULITIS</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>NOCARDIOSIS</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>HISTOPLASMOSIS</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>PML –VZV+JCV</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>GRANULOMA</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>ENCEPHALITIS VIH+VZV</td>
<td>1</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

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Diagnosis
N=300

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma G IV</td>
<td>5</td>
<td>1.7%</td>
</tr>
<tr>
<td>Glissarcoma</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Oligodendrogliaoma</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Brain Stem MTS</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>Incharacteristic Findings</td>
<td>25</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
CNS lymphoma

- High incidence (1-10-12%)
- Most frequent non-infectious disease found in AIDS patients
- Incidence: 2.7% in clinical series and 1-15% in autopsies
CNS lymphoma

- Related with immunosuppression
- High grade, diffuse B-cells Tumors
- Multiple and bilateral
- Related with Epstein Barr Virus
- Single periventricular lesions
- Multiple infra and supratentorial lesions
- MRI Spectroscopy: high coline, low NAA and presence of fat and lactate
35 years old male, headaches and seizures
CD4 < 50 cells
28 years old male, right hemiparesia and seizures
CD4 < 50 cells
25 years old female, seizures and headaches
CD4 < 50 cells
CNS lymphoma
CNS lymphoma
CNS lymphoma
CNS lymphoma
CNS lymphoma

- Lymphoid cells in the perivascular space
PCR - Epstein Barr
- Circulating Epstein-Barr virus (EBV) in HIV-infected patients and its relation with primary brain lymphoma


- Epstein-Barr virus genotypes and LMP-1 variants in HIV infected patients

Glucocorticoid therapy obscures the diagnosis of cerebral lymphoma

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\textsuperscript{1} Institut für Pathologie and \textsuperscript{2} Abteilung für Stereotaktische Neurochirurgie, Universitäts-Klinikum, Universität des Saarlandes, D-6650 Homburg, Federal Republic of Germany

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TOXOPLASMOSIS
47 years old male, headaches and focal symptoms, CD4 < 50 cells

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Chagas disease

- Meningoencephalitis
- Brain Chagomas
32 years old male, headaches and left hemiparesia, CD4 < 50 cells
24 years old male, headaches. CD4 < 50 cells
55 years old male. seizures
CD 4 < 50 cells
Chagas disease
Chagas disease
Chagas disease
Chagas disease
Chagas disease
Chagas disease
Chagas disease
Chagas disease

Trypanosoma in blood and CSF samples
Chagas disease

Meningoencephalitis with free amastigotes in brain smear, Anti-chagas policlonal antibody immunoreactivity. 400 X
Tuberculosis

- Meningoencephalitis
- Brain Tuberculomas
- Brain Abscess
- Vasculitis
Tuberculosis

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Tuberculosis
Tuberculosis

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Tuberculosis
Vasculitis

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Criptococciosis

- Meningoencephalitis
- Criptococcomas
- Soap bubble lesions
Criptococcosis
Nocardia
Nocardia Absesus
Gliosarcoma

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Fig. 1: Fusocellular Tumor with mitosis. HE 200 X
Fig. 2: Fusocellular Tumor, positive immunomarcation for Vimentine. 400 X
Fig. 3: Fusocellular Tumor, negative immunomarcation for GFAP. 400 X
Oligodendroglioma

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Brain stem metastasis
Progressive Multifocal Leukoencephalopathy (JCV)
PML

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PML

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PML

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PML: Cell with an intranuclear inclusion body. Inclusion in EPON. 1000 X

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PML ( JCV + VZ )
PML ( JCV + VZ )
PML( JCV + VZ )
PML( JCV + VZ )
STEREOTACTIC BIOPSY IN AIDS PATIENTS
(N = 300)

- 37% contrast enhancement
- 63% no enhancement
BIOPSIAS ESTEREOTÁCTICAS EN PACIENTES HIV + (N = 262)

Lesiones que captan contraste (N = 161)

- Linfoma: 51%
- Chagas: 26%
- Toxoplasmosis: 9%
- Mts. Ca.: 1%
- Gliomas: 3%
- INC: 4%
- Cripto: 4%
- TBC: 4%
BIOPSIAS ESTEREOTÁCTICAS EN PACIENTES HIV+ (N = 262)
Lesiones que no captan contraste (N = 101)

- ENCEFALITIS 13%
- GLIOSIS 17%
- TOXO 6%
- LMP 61%
- LINFOMA 2%
The Changing Pattern of HIV Neuropathology in the HAART Era

FRANÇOISE GRAY, MD, PhD, FABRICE CHRÉTIEN, MD, ANNE VALÉRIE VALLAT-DECOUVELAERE, MD, AND FRANCESCO SCARAVILLI, MD, PhD

Abstract. Highly active antiretroviral treatment (HAART), which has been available for most AIDS patients in France since 1996, has resulted in a dramatic improvement of the progression of the disease. From the survey of our series of 343 brains with acquired immunodeficiency syndrome (AIDS) from patients who died between 1985 and 2002, we found both quantitative and qualitative changes in the pattern of human immunodeficiency virus (HIV) neuropathology. Quantitatively, despite a dramatic decrease in the number of autopsies, brain involvement remained a major cause of death. There was an overall decrease in incidence of cerebral toxoplasmosis, cytomegalovirus encephalitis (CMVE), and HIV encephalitis (HIVE), for which successful treatment is available. This contrasted with the unchanged incidence of progressive multifocal leukoencephalopathy (PML) and malignant non-Hodgkin lymphomas (MNHL). However, when looking closer at the 3 last years, the incidence of diseases affecting patients with severe immunodepression (CMVE, PML, and MNHL) decreased between 2000 and 2002, whereas infections occurring in patients with milder immunodeficiency, toxoplasmosis, varicella-zoster encephalitis (VZVE), or herpes simplex virus encephalitis (HSV)E became more frequent. In addition, we found uncommon types of brain infection such as BK virus encephalitis or general paresis. Finally, we described new variants of HIV: severe leukoencephalopathy with intense perivascular macrophage and lymphocyte infiltration, possibly due to an exaggerated response from a newly reconstituted immune system, and chronic “burnt out” forms of HIVE as VZVE, toxoplasmosis, or PML, possibly associated with prolonged survival, in which neither inflammation nor organisms could be detected. These findings are compared with those reported in other neuropathological studies from different developed countries.

Key Words: Acquired immunodeficiency syndrome (AIDS); Central nervous system; Highly active antiretroviral treatment (HAART); Human immunodeficiency virus (HIV); Neuropathology.
Complications (N=300)

• Morbidity: 5 patients (1.7%)
• Mortality: 2 patients (0.7%)
Results (N=300)

Over 300 procedures we arrived to a diagnosis (histology/bacteriology/virology) in 275 patients

DIAGNOSTIC YIELD : 91.7%

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Conclusions

• Neuroradiology, as well as serologic, or csf analysis are useful but they cannot make a patognomonic diagnosis
• Antiretroviral treatment can be started if you find desmielinization in MRI with JCV in CSF (PML)
• AIDS patients with CNS lesion, atypical for toxoplasmosis or with bad response to anti toxo treatment are suitables for a stereotactic biopsy
• **Cooperation among different medical disciplines lead to a better diagnose and prognostic for those patients**
Thank you.
SEE YOU IN ARGENTINA!

Claudio G. Yampolsky M.D.