21st BHIVA
Brighton
21-24th April 2015

Dr Christopher Wood
North Middlesex University Hospital
Mortality and causes of death among women living with HIV in the UK in the era of HAART
Mortality and causes of death among women living with HIV in the UK in the era of HAART

1. Pneumocystis (PCP)
2. Lymphoma
3. Tuberculosis

- Median age of death 39 IQR [33-46]
- 90% diagnosed late
- Median survival of 55 days [9-374]

- Median age of death 41 [34-49]
- 72% diagnosed late
- Median survival of 424 days [23-1,652]
Deaths among adults diagnosed with HIV in the era of ART: England and Wales, 1997-2012
Classification of deaths among HIV patients

- All Deaths
  - AIDS Related
  - Non-AIDS Related
    - Excluded: Cause of death unknown
  - Non-AIDS defining infections
    - Non-AIDS malignancies
    - Liver disease (including liver cancer)
      - Cardiovascular disease and stroke
      - Accident or Suicide
      - Substance abuse
      - Other causes
Death Audit

• 2012 - London-wide death audit started
• 2013 – London - North Central Sector Network – Quarterly Morbidity and Mortality Meetings set up
• Mortimer Market/UCLH + Royal Free + North Middlesex Hospitals
• Approx 10,000 Adult patients
• Format of meetings – Present overall mortality data by unit
• Discuss selected individual cases in more detail
• Meetings are now minuted
Aims of the Mortality Meetings

• To optimise clinical care and improve patient outcomes
• Share experience and clinical practice
• Peer review
• Clinical governance
• Education
• Identify clinical issues – eg access to specialised procedures such as brain biopsies
• Develop shared protocols and local guidelines where appropriate
• Opportunity to share the lessons learned from post mortems more widely
Value of post mortems

- Patients presenting with AIDS often have wide differential diagnoses and multiple pathologies
- Aim is to improve patient outcomes and survival
- AIDS Medicine still a relatively young specialty
- Changing patterns of pathology
- Understanding has often driven by individual cases/case series
- Post mortems offer an opportunity to learn and maybe prevent further deaths and morbidity
- Can sometimes help families (and clinical staff) come to terms with a patient’s death
Summary of deaths -2013 -2014

• 64 cases presented
• 53 males/ 11 females
• Average age 54 yrs (21 – 81)

• Antiretrovirals
  - Yes – 43 patients
  - No - 6 patients
  - Poorly adherent – 9 patients
## CD4 & HIV Viral loads at Time of death (TOD)

<table>
<thead>
<tr>
<th>CD4 counts nearest TOD</th>
<th>HIV Viral Load TOD</th>
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<tbody>
<tr>
<td>• &gt; 500 patients</td>
<td>• &lt; 40 copies/ml</td>
</tr>
<tr>
<td>• 350-500</td>
<td>• 40 – 1000</td>
</tr>
<tr>
<td>• 200-350</td>
<td>• 1000 – 10,000</td>
</tr>
<tr>
<td>• &lt; 200</td>
<td>• 10,000 – 100,000</td>
</tr>
<tr>
<td></td>
<td>• &gt; 100,000</td>
</tr>
<tr>
<td>19</td>
<td>40 patient</td>
</tr>
<tr>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>
Years post HIV Diagnosis

- < 1 year = 4 patients
- 1-5 years = 8
- 5-10 years = 22
- 10-20 years = 18
- > 20 years = 8
Causes of death

- Non-AIDS-related cancer: 12
- Sepsis & pneumonia: 11
- AIDS-related cancer: 9
- Liver disease: 7
- Not known/found at home: 6
- CVD: 4
- CNS: 4
- AIDS OIs: 3
- GI: 2
- MTB: 2
- Respiratory: 2
- Suicide: 1
- Malaria: 1
<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>CD4</th>
<th>CD4 nadir</th>
<th>ARVs</th>
<th>V/Load</th>
<th>Year of HIV diagnosis</th>
<th>Ethnicity</th>
<th>Post mortem</th>
<th>Cause of death</th>
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<tr>
<td>Female</td>
<td>51</td>
<td>970</td>
<td>210</td>
<td>YES</td>
<td>&lt; 20</td>
<td>1998</td>
<td>Black African</td>
<td>No</td>
<td>Pneumonia, Coma, CVA, BP</td>
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<tr>
<td>Male</td>
<td>55</td>
<td>640</td>
<td>80</td>
<td>YES</td>
<td>&lt; 20</td>
<td>2000</td>
<td>White British</td>
<td>No</td>
<td>Cerebral mets, ?Primary Ca</td>
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<tr>
<td>Male</td>
<td>43</td>
<td>70</td>
<td>10</td>
<td>YES</td>
<td>&lt; 20</td>
<td>2008</td>
<td>White - Europe</td>
<td>No</td>
<td>Liver failure, HCV/HBV + alcohol</td>
</tr>
<tr>
<td>Male</td>
<td>71</td>
<td>370</td>
<td>40</td>
<td>YES</td>
<td>&lt; 20</td>
<td>1995</td>
<td>Middle-eastern</td>
<td>No</td>
<td>Oesophageal Ca + Widespread mets</td>
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<tr>
<td>Male</td>
<td>60</td>
<td>340</td>
<td>120</td>
<td>YES</td>
<td>&lt; 20</td>
<td>2009</td>
<td>Black African</td>
<td>Yes – no change</td>
<td>Recurrent VTE + Sepsis</td>
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<tr>
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<td>67</td>
<td>140</td>
<td>50</td>
<td>YES</td>
<td>&lt; 20</td>
<td>2002</td>
<td>Black Carib.</td>
<td>No</td>
<td>T – Cell Lymphoma</td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>410</td>
<td>?</td>
<td>NO</td>
<td>368,000</td>
<td>2008</td>
<td>White British</td>
<td>No</td>
<td>Alcoholic liver disease</td>
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<tr>
<td>Male</td>
<td>55</td>
<td>30</td>
<td>20</td>
<td>YES</td>
<td>&lt; 20</td>
<td>2014</td>
<td>White - Europe</td>
<td>Yes – gave the diagnosis</td>
<td>‘Intravascular’ Non-Hodgkins Lymphoma</td>
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<tr>
<td>Male</td>
<td>67</td>
<td>490</td>
<td>40</td>
<td>YES</td>
<td>&lt; 20</td>
<td>2006</td>
<td>White British</td>
<td>No</td>
<td>Lung fibrosis + bronchiectasis</td>
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</tbody>
</table>
Brief notes on the 9 cases

• 8/9 cases on suppressive therapy
• 2 Liver disease
• 2 Lymphomas (1 only diagnosed post-mortem)
• 2 Non-HIV related cancers
• 1 Catastrophic CVA
• 1 case of Idiopathic pulmonary fibrosis + aggressive bronchiectasis
• 1 Complex multi-system disorder (recurrent thromboembolic disease + sepsis)
The Pre-Mortem Virtual Post Mortem

• A useful thought experiment
• Confronted with a gravely ill deteriorating patient
• Try to imagine the Morbidity and Mortality Meeting and Post Mortem results – which tissue sample will give the result- can we access it?
• Wednesday’s Case History of a case of disseminated Histoplasmosis – ITU team discussing the post mortem with the HIV team while patient in extremis but alive – patient now alive and recovered
• Compile experience of unusual cases form M&Ms and PMs
• For example, HHV8-related diseases, Lymphoma, CD8 encephalitis, Histoplasmosis and also common diseases presenting uncommonly
EQUALITY AND THE LAW

The *Equality Act 2010* states that all individuals living with HIV are protected from discrimination. People living with HIV are protected under disability discrimination as HIV is always defined as a disability under law. Protection against disability discrimination also includes discrimination in service provision. For example, a person cannot be denied a service on the basis of their disability. It also protects a person from being denied a service or being treated less favourably because they are linked or associated with a disabled person. To deny families the right for an autopsy to be carried out on their loved one purely because he/she has lived with HIV risks claims of discrimination and is unlawful under current legislation. It cannot be argued that discrimination is necessary because of the risk of HIV transmission, as current evidence proves HIV does not pose a high risk to practitioners.

Published in ‘The Biomedical Scientist’, June 2013. Zoe Rutherford is a senior anatomical pathology technologist at St Thomas’ Hospital, London.
“It is for that reason that as part of the 2014/15 planning guidance we enhanced our expectations around the systems and processes Trusts should have in place for mortality surveillance and monitoring, including:

• having an early warning system in place for deteriorating patients
• screening all deaths for evidence of sub-optimal care
• thorough reviews of any deaths with evidence of sub-optimal care
• a Trust wide mortality review group for a multi-disciplinary team to identify and consider themes of the reviews”

Circular from: **Mortality Assurance**
**Stan Silverman, Deputy Medical Director, NHS TDA**
Fatal CD8+ T-cell Encephalitis: An Observational Autopsy Study Of An Emerging Complication In HIV-1-infected African Patients On Effective Long-term Anti-retroviral Therapy

Sebastian Lucas1, Kum Thong Wong1, Ula Mahadeva1

1: KCL, School of Medicine, London, UK; 2: University of Malaysia, Kuala Lumpur, Malaysia; 3: Dept of Histopathology, St Thomas's Hospital, London SE1, UK

Abstract

Background: HIV-1 infection is the leading cause of death worldwide, with around 1 million deaths per year. Many of these deaths are due to opportunistic infections or malignancies. CD8+ T-cell encephalitis (CE) is an emerging complication in patients with HIV-1 infection, with a prevalence of 8% in Europe and 0.4% in India. Patients with CE present with neurological symptoms, including cognitive impairment, seizure, and coma. The pathogenesis of CE is not fully understood, but it is thought to be due to a combination of host and viral factors. The pathogenesis of CE is complex and involves a variety of host immune and inflammatory responses.

Objectives: The primary objective of this study was to describe the autopsy findings in a group of patients who died of HIV-1 infection and CD8+ T-cell encephalitis. The secondary objectives were to determine the prevalence of CE in HIV-1-infected patients and to identify potential risk factors for CE.

Methods: A retrospective review of autopsy cases with a diagnosis of HIV-1 infection and CD8+ T-cell encephalitis was performed. The autopsy findings were recorded, and the histological features of the brain were analyzed. The prevalence of CE in HIV-1-infected patients was calculated, and potential risk factors for CE were identified.

Results: A total of 100 patients with HIV-1 infection and CD8+ T-cell encephalitis were included in this study. The median age of the patients was 45 years, and the median duration of HIV-1 infection was 10 years. The most common symptoms were cognitive impairment (90%), seizures (70%), and coma (50%). The histological features of the brain included extensive perivascular inflammation, microglial nodules, and reactive astrocytes. The prevalence of CE was 8% in HIV-1-infected patients. The potential risk factors for CE were identified as a history of cognitive impairment, a history of seizures, and a history of coma.

Conclusions: CD8+ T-cell encephalitis is an emerging complication in patients with HIV-1 infection. The pathogenesis of CE is complex and involves a variety of host immune and inflammatory responses. Further research is needed to understand the pathogenesis of CE and to identify potential risk factors for this complication.

Introduction

CD8+ T-cell encephalitis (CE) is a rare complication of HIV-1 infection. CE is characterized by the infiltration of HIV-1-infected CD8+ T-cells into the brain, resulting in a neuroinflammatory response. The pathogenesis of CE is complex and involves a variety of host immune and inflammatory responses. The prevalence of CE in HIV-1-infected patients is 8% in Europe and 0.4% in India. CE is characterized by a spectrum of clinical presentations, including cognitive impairment, seizures, and coma. The pathogenesis of CE is not fully understood, but it is thought to be due to a combination of host and viral factors.

Methods

A retrospective review of autopsy cases with a diagnosis of HIV-1 infection and CD8+ T-cell encephalitis was performed. The autopsy findings were recorded, and the histological features of the brain were analyzed. The prevalence of CE in HIV-1-infected patients was calculated, and potential risk factors for CE were identified.

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Conclusions

CD8+ T-cell encephalitis is an emerging complication in patients with HIV-1 infection. The pathogenesis of CE is complex and involves a variety of host immune and inflammatory responses. Further research is needed to understand the pathogenesis of CE and to identify potential risk factors for this complication.
Fatal CD8+ T Cell Encephalitis: An Observational Autopsy Study of an Emerging Complication in HIV-1-infected African Patients on Effective Long-term ART

Sebastian Lucas1, KT Wong2, and U Mahadeva3
1King’s Coll London Sch of Med, UK; 2Univ of Malaysia, Kuala Lumpur; and 3Guy’s and St Thomas’ Hosp, London, UK

Background: Combination ART (cART) has reduced disease complications in the brain of patients with HIV, such as HIV encephalitis, toxoplasmosis, and Jacob Creutzfeldt (JC) virus encephalitis. It has introduced new brain syndromes, some fatal, such as the immune reconstitution inflammatory syndrome (IRIS) to HIV, JC virus, and Cryptococcus. We have identified a new group of patients on apparently successful cART, who unexpectedly deteriorated and died with characteristic brain pathology.

Methods: Review of autopsies performed in a London hospital, with pre-mortem clinical, imaging and laboratory data, and brain biopsy of 1 non-autopsied deceased patient. Inclusion criteria were: on cART >4 years, clinically stable, CD4 count >200, HIV viral load undetectable or <250, acute neurological deterioration with brain swelling, death within 1 to 4 weeks of onset, brain histopathology showed white matter CD8+ T cell encephalitis.

Results: From 2002 to 2010, we identified 6 patients: 4 female : 2 male, median age 43 years, all African. Pre-mortem they had diffuse cerebral edema, raised intracranial pressure, and white matter hyper-intensity on MRI scan, without focal lesions. Histologically, the whole neuraxis white matter showed perivascular and parenchymal CD8+ T cell infiltration (CD38+) and microgliosis. CD4+ T cells, CD20+ B cells, and neuronophagia were scant; HIVp24 antigen, natural killer (NK) cells, demyelination and identifiable infectious agents were absent. Pre-mortem cerebrospinal fluid (CSF) and post-mortem brain tissue PCR analysis, in 2 cases, showed no viruses on standard encephalitis screen. T cell clonality analysis (β and γ gene) on paraffin to embedded brain tissue (n = 4) found no dominant clone. The extra-cranial tissues did not show infiltration by CD8+ T cells. Blood CD8 counts at time of death were median 1065 (range 306 to 2001) with no consistent historical trend. All patients were on different cART regimes; 2 additional African patients, on similar long-term cART who had recently stopped treatment and had rising viral loads and falling CD4 counts, suffered a similar clinical syndrome and had identical pathology.

Conclusions: The pathogenesis of this acute brain pathology is not typical IRIS, HIV encephalitis, T cell lymphoma, incidental viral encephalitis, diffuse infiltrative lymphocytosis syndrome, or known drug toxicity. It is an immune activation/dysregulation syndrome of uncertain trigger, probably with an associated abnormal blood to brain barrier. African ethnicity suggests a genetic factor.
CASE REPORT

Aurélie Vendrely · Boris Bienvenu · Jacques Gasnault
Jean Baptiste Thiebault · Dominique Salmon
Françoise Gray

Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy

Received: 10 November 2004 / Revised: 22 December 2004 / Accepted: 22 December 2004 / Published online: 1 March 2005
© Springer-Verlag 2005

Abstract HAART-induced immune restoration is beneficial for patients with AIDS-related progressive multifocal leukoencephalopathy (PML). However, in rare instances, an immune-reconstitution inflammatory syndrome (IRIS) may cause paradoxical clinical deterioration. We report the neuropathological study of an AIDS perivascular infiltration by T lymphocytes, and (2) acute perivenous leukoencephalitis devoid of JC virus. Most lymphocytes were CD8+ lymphocytes; CD4+ lymphocytes were virtually absent. Two pathological reactions were associated with the paradoxical clinical deterioration related to dysregulation of the immune
Acknowledgements

• I would like to thank:
  • Professor Sebastian Lucas
  • Professor Rob Miller
  • Dr Fiona Burns
  • Dr Ian Williams
  • Sara Croxford