

“Then and now”- a thirty-year perspective

Rob Miller

24 April 2015

What happened in 1985?

07 Jan =Lewis Hamilton, F1 driver born

19 Feb =First episode of EastEnders shown

11 Mar =Mohamed Al-Fayed buys Harrods

13 Jul ='Live Aid' concerts in London & Philadelphia

01 Sep =Wreck of the Titanic is discovered

28 Sep =Brixton riots

02 Oct =Rock Hudson dies of AIDS

20 Nov =First version of Windows is released

Also that year =first use of DNA in a criminal case

Causes of death 1984-86

PCP

PCP + pneumothorax, post TBB

PCP + pulm haemorrhage, post TBB

PCP + PKS

Severe pneumonia (presumptive PCP)

Disseminated KS + resp failure (presumptive PKS)

Wasting + high volume (cryptosporidial) diarrhoea

Wasting + CMV retinitis

Disseminated NHL

1984-86

Sporadic PMs

Done at St Stephen's hospital

Reports slow to be sent

Never got histology information

Didn't add hugely to knowledge and understanding

No good interaction with an “interested” pathologist

Often mis-interpreted what we observed/described

Respiratory Medicine (1990) **84**, 409–411

Cavitory lung disease caused by *Mycobacterium avium-intracellulare* in AIDS patients

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1984-86

Increasing awareness:

Reports from USA

eg Nash G, Fligiel S Am J Clin Pathol 1984; 81:6-12

What clinically known/suspected in life ≠ findings at PM

Majority had >1 diagnosis

(Hickam's dictum vs Ocam's razor)

Novel presentations of disease

eg Hodgkin lymphoma exclusively in BM

AUTONOMIC NEUROPATHY IN AIDS

SIR,—Dr Craddock and colleagues (July 4, p 16) describe autonomic neuropathy associated with AIDS and HIV infection. We have seen a patient with AIDS who had an autonomic neuropathy in association with a dementing process and parkinsonism.

A 53-year-old anti-HIV positive homosexual man presented with *Pneumocystis carinii* pneumonia. He had severe postural hypotension. He also had a mask-like face with paucity of facial expression, generalised bradykinesia, and "lead pipe" rigidity. There was evidence of dementia, with loss of short-term memory and disorientation in time and place. There was no peripheral

This patient had evidence of an autonomic neuropathy and parkinsonism and dementia, features reminiscent of Shy-Drager syndrome. We propose that multisystem atrophy be added to the list of neurological manifestations of AIDS.

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“One thing I have learned from our series of over 40 AIDS autopsies is that experience from other autopsies has not really prepared me for what I see in these cases – with such bizarre presentations of lesions that we have rarely seen before in the general population”

“Virtually everything I saw macroscopically at autopsy in this man I guessed incorrectly”

Clinico-pathological conference

Metastatic cerebral lymphoma

L Hughes-Davies, M Spittle, M J Harrison, S B Lucas, R F Miller

Disseminated *Pneumocystis carinii* infection in AIDS

R J Coker, D Clark, E L Claydon, M Gompels, J G Ainsworth, S B Lucas, R Miller, R D F Goldin, A J Pinching, J R W Harris

Abstract

Eight patients with AIDS and *Pneumocystis carinii* infection were studied. Protean manifestations were a feature not untypical of disseminated pneumocystosis. Aerosolised pentamidine as prophylaxis against *P carinii* pneumonia was ineffective at suppressing dissemination. The knowledge that extrapulmonary infection can occur has implications for the detection and

CASE 2

A 26 year old homosexual man presented with severe abdominal pain. A chest x ray picture on admission showed bilateral pulmonary infiltrates suggestive of *P carinii* pneumonia. He had been found to be HIV antigen and antibody positive two years previously (November 1988). *Mycobacterium malmoense* had been isolated from sputum samples in June 1990 and at that time he had started quadruple anti-tuberculous treatment. He had developed

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Premature bullous pulmonary damage in AIDS

R F Miller, S J G Semple, S B Lucas

Case report (Dr R F Miller)

A 31 year old Caucasian man was admitted to this hospital for investigation of fever, progressive weight loss and cavitating lesions on his chest radiograph. The patient was a business man, he was homosexual and denied intravenous drug abuse. He smoked 30 cigarettes per day and drank 2 units of alcohol per week.

His past medical history began in 1977 when he suffered from rectal gonococcus. In 1984 he developed oral candidiasis. Later on in 1986 he requested an HIV test. Following counselling he was found to be HIV-1 antibody positive. At this time he

tive *Pneumocystis carinii* pneumonia with nebulised pentamidine. After 2 weeks treatment there had been no response, so the patient proceeded to fibre-optic bronchoscopy. At bronchoscopy the endobronchial appearances were normal. Transbronchial biopsy was attempted but was unsuccessful. Broncho-alveolar lavage fluid was smear-positive for AAFB. In addition cytoplasmic inclusions were seen and thought to represent cytomegalovirus infection. Culture of the lavage fluid, however, revealed no evidence of cytomegalovirus, and atypical mycobacteria were seen, thought possibly to be *Mycobacterium kansasii*. A sample was sent to the reference

Clinico-pathological conference

Adult respiratory distress syndrome complicating *Pneumocystis carinii* pneumonia

A Scouler, J Moxham, S B Lucas, R F Miller

Case report (Dr A Scouler)

This 34 year old man presented with a 3 week history of fever, dry cough and exertional dyspnoea. He had returned from holiday in Madeira only 2 days previously. He was a non-smoker and drank alcohol moderately. In the past he had been treated for syphilis in 1974. At that time he also had genital herpes. He remained well until 1980 when he presented with acute hepatitis A and was also found to be hepatitis B immune, with positive anti-core and anti-surface antibodies. In September 1988 he presented with cutaneous lesions of Kaposi's sarcoma and was found to be HIV-1 antibody positive. He com-

Kaposi's sarcoma. His heart rate was 84 per minute, his blood pressure was 110/70 mm Hg and he had a respiratory rate of 18 per minute. Auscultation of the chest revealed no significant abnormalities and the rest of the examination was normal. On admission a chest radiograph was performed (fig 1). This showed bilateral interstitial shadowing in the upper zones, the mid and lower zones were relatively clear. Investigations showed he was anaemic with a haemoglobin of 8.9 g/dl; the white cell count was $1.8 \times 10^9/l$ with 50% neutrophils. Arterial blood gases taken breathing air showed a PO₂ of 12.1 kPa and a PCO₂ of 3.9 kPa. Blood cultures, urea and

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Metastatic cerebral lymphoma

L Hughes-Davies, M Spittle, M J Harrison, S B Lucas, R F Miller

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HIV-associated dilated cardiomyopathy

R F Miller, R Gilson, C Hage, F Scaravilli, L Michaels

Case Report (Dr R F Miller)

The patient was a 39 year old male homosexual book publisher. He first presented to this hospital in December 1988 with a diagnosis of oral hairy leukoplakia and at the time was found to be HIV 1 antibody positive and to be hepatitis B immune. Not long after this he developed a cough, increasing exertional dyspnoea and a reduced exercise tolerance. He was admitted for investigation in January 1989. A chest radiograph showed bilateral infiltrates

he reported subjective memory loss and also some episodes of confusion which were short lived. Despite these symptoms he was continuing to work full-time and continued to do so over the next 16 months.

In October 1990 he was again admitted as an emergency. He had just returned from holiday in Spain and had become confused and incoherent and then had three grand mal fits. On examination he had generalised hypertonia and hyperflexia. He was unconscious with no focal neurological signs; he

Comparison of magnetic resonance imaging with neuropathological findings in the diagnosis of HIV and CMV associated CNS disease in AIDS

R F Miller, S B Lucas, M A Hall-Craggs, N S Brink, F Scaravilli, R J S Chinn, B E Kendall, I G Williams, M J G Harrison

Abstract

Objectives—To compare the results of clinical assessment and MRI with neuropathological findings in the diagnosis of HIV and cytomegalovirus (CMV) associated CNS disease.

Methods—A retrospective study of 35 patients infected with HIV who were examined at necropsy between four and 70 (median 20) days after neurological assessment and MRI.

associated with a range of neuropathological changes including diffuse myelin pallor (HIV leukoencephalopathy), and encephalitis.⁶ The clinical presentation may be difficult to distinguish from the subacute or chronic encephalitis caused by cytomegalovirus (CMV)⁷ and neuroimaging and CSF studies are of uncertain value in differentiating CMV encephalitis and HIV leukoencephalopathy/encephalitis.

Several studies have reported the clinicopathological correlates of these conditions and

CASE REPORT

Robert F. Miller · Michael J. G. Harrison
Margaret A. Hall-Craggs · Francesco Scaravilli

Central pontine myelinolysis in AIDS

Received: 6 March 1998 / Revised, accepted: 11 May 1998

Abstract Central pontine myelinolysis (CPM) is an uncommon complication in sick patients with severe underlying disorders such as chronic alcoholism, malignancy, malnutrition and hyponatraemia. We report two patients with advanced HIV infection who developed CPM. In one case the diagnosis was not suspected in life, in the other the diagnosis was made just before death, on the basis of magnetic resonance (MR) imaging appearances. At post mortem there was a close correlation between the MR abnormalities and the anatomic changes in the pons.

ity in adults, and invariably associated with severe underlying disorders including chronic alcoholism, chronic renal failure treated with dialysis, hepatic failure, advanced lymphoma, carcinoma, cachexia and malnutrition from a variety of causes, severe bacterial infections, dehydration, burns and hyponatraemia (and its rapid correction) [5, 7, 13, 14].

The clinical presentation varies between rapidly evolving spastic paraparesis with pseudobulbar palsy, and changes in mental state with confusion or coma. Some

Herpesvirus infection of eye and brain in HIV infected patients

Robert F Miller, Mark R Howard, Peggy Frith, Christopher J Perrons, Irene Pecorella, Sebastian B Lucas

Objectives: To compare histological with genome detection methods for diagnosis of herpesvirus infection in eye and brain of HIV infected patients undergoing necropsy and to correlate these findings with both antemortem clinical findings and postmortem evidence of extraocular herpesvirus infection, especially in the CNS.

Methods: A prospective study of 31 consecutive HIV infected patients undergoing necropsy. In life 11 patients had been assessed by an ophthalmologist because of ocular symptoms. Ocular and brain samples were examined for herpesviruses by conventional histological methods and by nested polymerase chain reaction (nPCR) for all eight human herpesviruses; evidence of extraneuronal herpesvirus infection was sought by histological methods.

Robert F. Miller · Peter G. Isaacson
Margaret Hall-Crags · Sebastian Lucas
Françoise Gray · Francesco Scaravilli · Shu F. An

Cerebral CD8+ lymphocytosis in HIV-1 infected patients with immune restoration induced by HAART

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Abstract In HIV infected persons, highly active antiretroviral therapy (HAART) has reduced both the morbidity and incidence of several disorders. Its effects on direct HIV-induced damage to the CNS remain controversial. In addition, HAART may provoke an “immune reconstitution inflammatory syndrome” (IRIS). Herein we report two patients who, despite HAART, developed a diffuse encephalopathy. Their clinical, radiological and neuropathological features are described. Immunohistochemical and PCR analyses were used to detect HIV and to exclude

other viruses in brain tissue. The unusual inflammatory reaction in the brain tissue was defined by immunohistochemistry. Both patients had advanced HIV disease with low CD4 counts and high HIV “viral loads” before starting HAART. In both, HAART induced an increase in CD4 count and a marked reduction in HIV viral load, which was accompanied, in patient one, by worsening of pre-existing, and, in patient two, by development of, acute encephalopathy. At post-mortem examination, the brain of patient one showed HIV encephalitis. In addition, the brains of both patients revealed HIV-DNA by PCR, diffuse microglial hyperplasia and massive and diffuse perivascular and intraparenchymal infiltration by CD8+/CD4+ lymphocytes. We suggest that the rapid immune reconstitution induced by HAART in these two patients led to a

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Review Article

Changing patterns of human immunodeficiency virus-associated neuropathology

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Abstract

This paper describes the evolution of the pathogenic concepts associated with the infection by the human immunodeficiency virus (HIV), with emphasis to the pathology of the nervous system. Although the first description of damage to the nervous system in the acquired immunodeficiency syndrome (AIDS) only appeared in 1982, the dramatic diffusion of the epidemic worldwide, as well as the invariably rapidly fatal outcome of the disease before the introduction of efficient treatment, generated from the beginning an enormous amount of research and re-thinking on a number of pathogenetic concepts. Less than 25 years after the first autopsy series on AIDS

Recent frustrations (1)

42 year-old MSM

HIV+ 8 years; not engaged in care since diagnosis

PC ↓wt – 15kg/2 years

watery diarrhoea x20/day

epigastric pain on eating

fever +/- night sweats

Inx oesophageal/colonic Bx =ulceration/CMV inclusions

Cryptosporidial diarrhoea

CXR/SaO₂ =N

CD4 =10; VL >450 000

Recent frustrations (1)

Mx iv ganciclovir

oral opiates

ARVs

Prg 10/7 later → new respiratory symptoms

abn CXR/↓SaO₂

BAL = *P. jirovecii*; inflammation+++

IRIS PCP

Mx iv co-trimoxazole + prednisolone = recovered

3/52 gaining wt/diarrhoea settling

CD4 =30; VL 1500

diarrhoea worsening, Cryptosporidium in stool

Recent frustrations (1)

Prg 2/52 later → new onset focal seizures

MRI x1 ring-enhancing lesion L inf temp lobe
surrounding oedema
mass effect

Pt and family elected to withdraw care →
home

Pt keen for a PM! Family concurred
Died at home GP/PCT

Couldn't arrange for PM to be done

Dx 1° cerebral lymphoma?

IRIS?

Recent frustrations (2)

37 female N African origin

PC 3/12 progressive SOBOE

malaise

minor wt loss (<2kg)

OE clubbed

end-inspiratory crackles

SaO₂ (room air) 87%

Inx CXR =widespread interstitial changes

HRCT =interstitial fibrosis (IPF pattern)

& patchy ground glass shadowing

peripheral blood lymphopenia

Recent frustrations (2)

Inx BAL =*P. jirovecii* +++

HIV+; CD4 =60; VL =189 000

Rx iv co-trimoxazole + prednisolone

ARVs after 16/7

Prg initial improvement, then steady decline

HRCT review at ILD MDT at Brompton

Not for ECMO/immune modification

Died on ICU

PM HIV team obtained husband's consent for PM

Not actioned by ICU team

1a: pulmonary fibrosis

1b: PCP

2: HIV infection