Acta Neurochir (Wien) (2004) 146: 1071–1074
DOI 10.1007/s00701-004-0334-0

Acta Neurochirurgica
Printed in Austria

Brief Review

Central nervous system AIDS – related diseases

F. Antunes

Serviço de Doenças Infecciosas, Hospital de Santa Maria, Clínica Universitária de Doenças Infecciosas, Faculdade de Medicina de Lisboa, Instituto de Higiene e Medicina Tropical, Lisboa, Portugal

Published online July 26, 2004

Summary

The neurological complications of HIV contribute importantly to patient morbidity and mortality. Major common AIDS-related CNS diseases are ADC, metabolic encephalopaties, CMV encephalitis, TE, PCNSL, PML, criptococcal meningitis, and aseptic meningitis. After HAART, declines in incidence and improved outcome of several HIV-1 related opportunistic infections, including CNS-ADIs have been reported. The differential diagnosis of CNS complications of AIDS is routinely established according to temporal evolution, clinical data, and neuroradiological imaging. Combining neuroradiological imaging with the new CSF PCR tests may improve the diagnostic accuracy of some CNS-ADIs without the need of stereotactic brain biopsy, that may become limited to the situations where data remain conflicting.

Introduction

HIV and AIDS are pandemic and pose one of the greatest challenges to global public health. HAART has led to a dramatic decrease in HIV – associated morbidity and mortality. However AIDS-related opportunistic illnesses continue to occur. According to the WHO, 42 million of adults and children are estimated to be living with HIV/AIDS as of the end of 2002. HIV and AIDS is the leading cause of death in Africa and the fourth leading cause of death worldwide [1, 2]. Approximately 5 million new infections and 3.1 million of deaths occurred during 2002.

In the United States, AIDS incidence increased rapidly through the 1980s, peaked in the early 1990s, and then declined. As of 1996, sharp declines were reported in AIDS incidence and deaths, and AIDS prevalence in the United States continues to increase. The introduction of HAART during 1996 and 1997 led to this reduction in mortality and risk of AIDS [3].

Across Europe, the introduction and continued use of HAART has resulted in a decline of AIDS incidence [4]. The death rate across Europe dropped rapidly, and within two years of the widespread availability of HAART, the number of deaths were less than a fifth of that number before HAART became available [5].

In the EuroSIDA (the largest European HIV/AIDS cohort study), CNS diseases incidence decreased from 5.9 per 100 person-year in 1994 to 0.5 in 2002 [6]. This incidence decrease was similar to that of non-CNS diseases. In this EuroSIDA cohort, TE was the most frequent CNS disease diagnosed (48%), followed by ADC (26%), cryptococcosis (19%), PML (9%), FBL (2%), and PCNSL (1%). The lowest annual decrease of incidence observed was for PML (31%), and the highest for PCNSL (48%).

Despite the reductions in the incidence of ADIs (tumours and opportunistic infections), the absolute rates of these diseases are still high [7].

The neurological complications of HIV infection are both common and varied, and they play an important role in patient morbidity and mortality. Disorders of CNS and of peripheral nervous system can cause complications in each stage of systemic HIV infection, from the period after initial infection through to the end stage of severe immunosuppression. The neurological complications can be classified in a number of ways. One classification, useful for analysis of individual

patients, is based on neuroanatomical localization [8]. Common major brain complications are ADC, metabolic encephalopaties, CMV encephalitis, TE, PCNSL and PML, and the common major meninges neurological complications are cryptococcal meningitis, and aseptic meningitis.

AIDS dementia complex

ADC develops later in the course of HIV-infection (before HAART 60% of the subjects developed ADC). Neuropsychological testing and neuroimaging procedures are essential for the evaluation of patients with CNS dysfunctions, in particular to rule out other conditions (for example, PCNSL). After HAART, a decline of 40–80% in the incidence of several individual HIV-1 related opportunistic infections have been reported. In Australia, the proportion of ADC increased from 5.2% in the years 1993–1995 to 6.8% in the years 1996–2000, however median survival increased, for the same periods of time, from 11.9 months to 48.2 months [9]. The improvement in median survival following ADC was approximately threefold greater than that for the other major CNS-ADIs. Despite declining ADC incidence, the prevalence of ADC appears to have increased in Australia since 1995. This trend is largely the result of the marked improvement in survival following ADC. An increasing number of people living with ADC indicate a continuing need for ADC treatment and care services. The search for better antiretroviral drugs that penetrate the blood-brain barrier must continue together with research on neuroprotective therapy to halt the long-term impact of persistent infection associated with inflammatory disease.

Toxoplasmic encephalitis

TE is the most frequent infectious cause of focal brain lesions, most of the cases arising from reactivation of latent infection. AIDS patients who have IgG anti-*Toxoplasma* and a CD4T lymphocyte count of less than 100 per μL have a 10–50% risk of developing TE [10]. The presumptive diagnosis of TE is established according to the clinical, neuroradiological imaging, serology for *Toxoplasma*, and the immunological status of the patient. However, there is no pathognomonic feature in the neuroradiological imaging, and 10–50% of the healthy adult population in the United States, and as many as 90% of adults in Europe and Africa are seropositive for *Toxoplasma* [11, 12]. In the case of clinical suspicion of TE, brain biopsy is generally indicated in patients with atypical CNS lesions, clinical deterioration during empirical therapy, and negative *Toxoplasma* serology. This invasive procedure has a 2–12% perioperative morbidity and a 2% associated mortality [13]. PCR test and the improvement in neuroimaging radiological techniques are recent progresses in the diagnosis of TE [14]. On the other hand recently discovered organelle (the apicoplast) and other parasite-specific metabolic pathways will result in the development of a range of new therapies in the near future [15]. In patients on HAART, primary and secondary prophylactic therapies for toxoplasmosis can be discontinued safely once the CD4T lymphocytes count is higher than 100 μL for more than three months [16].

Progressive multifocal leukoencephalopathy

PML is an opportunistic infection caused by JCV, the human polyomavirus that is usually non-pathogenic. Diagnosis often can be suspected clinically, whereas neuroimaging usually helps to support that, and rule out confounding diseases. White matter lesions showed in MR or CT scan could be confused with ADC lesions; however in PML the patient is worse than the scan, and in ADC the scan looks worse than the patient. Neither serum nor CSF are useful in the diagnosis (85–90% of general population have specific IgG antibodies) [17]. PCR detection of JCV DNA in CSF is useful for the diagnosis of PML. PCR detection of JCV DNA in blood and urine was considered a mark of active JCV infection, however 40% of healthy population and 16–38% of HIV-infected individuals excrete JCV in urine [18, 19]. Although there is no proven effective therapy for PML (use of systemic plus intrathecal cytarabine suggests that the drug has no rule in treating this disease), 7–9% of patients with AIDS-associated PML exhibit survival exceeding 12 months, and many remain stable or exhibit neurological recovery [20, 21]. According to several authors an improved outcome in PML has been correlated with the following: 1) PML occurring as the AIDS defining illness; 2) evidence of an inflammatory response to JCV as indicated by contrast enhancement of the lesions on radiographical imaging; 3) higher CD4T lymphocyte cell counts $>300/\mu l$ at the time of diagnosis; 4) the use of HAART with immune reconstitution associated to restoration of specific anti-JCV CD4 T-cell responses; 5) a low number or reduction in the JCV viral load in the CSF.

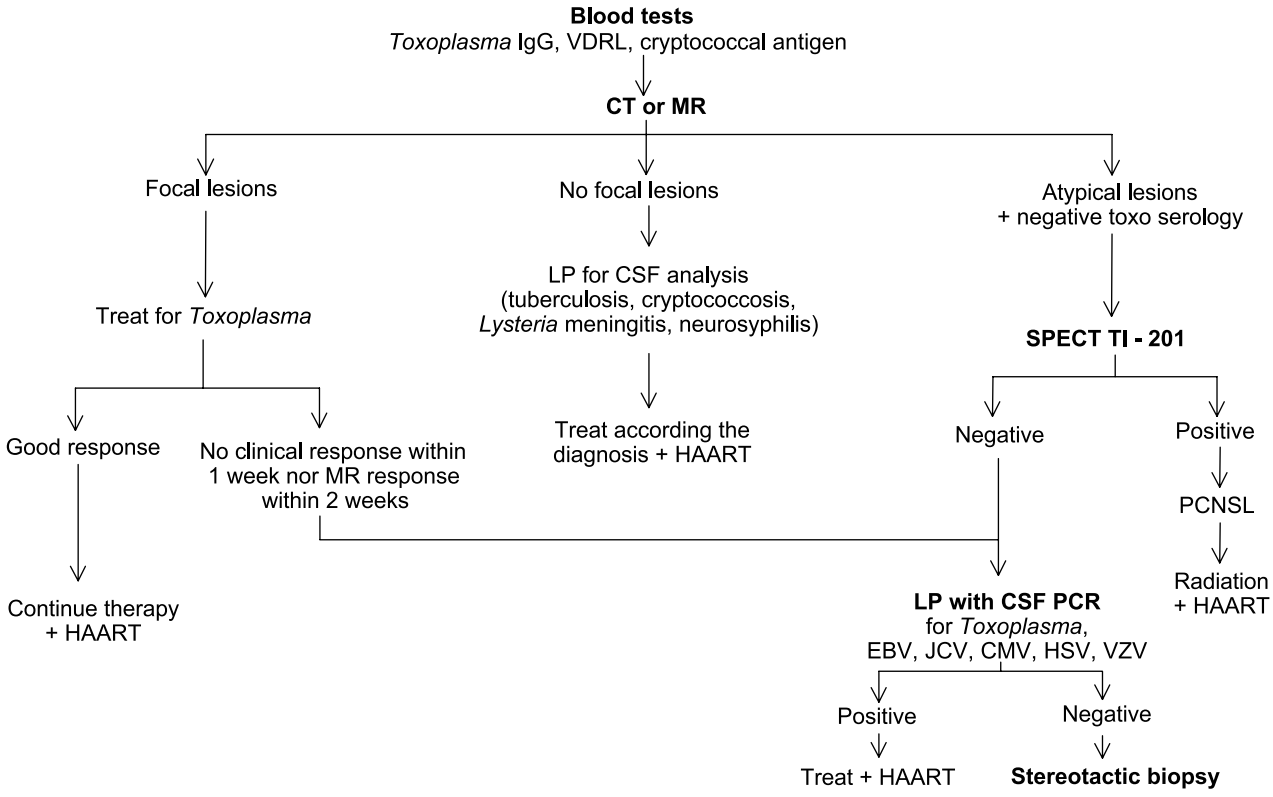

Fig. 1. Algorithm proposed for CNS evaluation in patients with advanced HIV infection

Primary central nervous system lymphoma

PCNSL is the second most common cause of focal brain disease in patients with AIDS, and presents with progressive focal or multifocal neurological deficits similar to those seen in TE or PML [22]. Diagnosis of PCNSL is established according the histology consistent with lymphoma, compatible MR, positive CSF EBV PCR and positive TI-201 brain SPECT [23, 24]. Receipt of HAART after PCNSL diagnosis is associated with a significantly longer survival in patients with AIDS-related PCNSL [25]. Given the apparent robust benefit of HAART, prompt diagnosis (CSF PCR for EBV and SPECT) may result in improved outcome. On the other hand the relative contribution of cranial radiation to survival needs to be determined in the HAART era, since it is associated with substantial side effects. Although chemotherapy was disappointing in the pre-HAART era and often associated with significant side effects, it may be effective in conjunction with HAART, radiation therapy and prophylaxis for opportunistic infections. Therapies that target EBV directly (zidovudine induces apoptosis in EBV-infected cells *in vitro*, and gancyclovir has activity against herpes virus), and immunotherapy (IL-2 improves immune reconstitution) should be studied [26, 27].

Presently, in most cases the differential diagnosis of these four common CNS complications of AIDS is established according to temporal evolution, clinical data, and neuroradiological imaging. However, neuroradiological imaging and CSF PCR tests may permit improvement of the diagnosis of some patients, and a reduction in stereotactic biopsy.

Figure 1 shows an algorithm proposed for CNS evaluation in patients with advanced HIV infection. Combining these techniques with the use of HAART could significantly improve survival in patients with these CNS ADIs.

Acknowledgments

I would like to express my thanks to two anonymous referees for constructive comments on the manuscript, Emília Valadas for review, David Hardisty for English review and Ana Sequeira for technical assistance.

Glossary of abbreviations

ADC AIDS dementia complex, *ADIs* AIDS-defining illnesses, *AIDS* acquired immunodeficiency syndrome, *CMV* human cytomegalovirus, *CNS* central nervous system, *CSF* cerebrospinal fluid, *CT* cerebral axial tomography, *DNA* deoxyribonucleic acid, *EBV* Epstein-Barr virus, *FBL* focal brain lesions, *HAART* highly active antiretroviral therapy, *HIV*

human immunodeficiency virus, *JCV* human polyomavirus JC, *LP* lumbar puncture, *MR* magnetic resonance imaging, *PCNSL* primary CNS lymphoma, *PCR* polymerase chain reaction, *PML* progressive multifocal leukoencephalopathy, *SPECT* brain single photon emission computerized tomography, *TE* toxoplasmic encephalitis, *TI-201* Thallium-201, *WHO* World Health Organization.

References

1. WHO (2002) Global situation of the AIDS pandemic, end 2002. Weekly Epidemiological Record 77(49): 417–424
2. WHO (2002) HIV/AIDS surveillance and global estimates. Weekly Epidemiological Record 77(50): 425–430
3. HIV and AIDS – United States, 1981–2000 (2001) MMWR; 50(21): 431–434
4. Kirk O, Mocroft A, Katzenstein TL *et al* (1998) Changes in use of antiretroviral therapy in regions of Europe over time. AIDS 12: 2031–2039
5. Mocroft A, Vella S, Benfield TL *et al* (1998) Changing patterns of mortality across Europe in patients infected with HIV-1: EuroSIDA study group. Lancet 352: 1725–1730
6. d'Arminio Monforte A, Cinque P, Mocroft A *et al* (2003) Changing incidence of central nervous system (CNS) AIDS-related diseases in the EuroSIDA sohort. Abstracts book of 9th European AIDS Conference (EACS), Warsaw, Poland. Abstract F916, p 19
7. Jones JL, Hanson DL, Dworkin MR *et al* (1999) Surveillance for AIDS – defining opportunistic illness, 1992–1997. MMWR CDC Surveillance Summ 48(SS-2): 1–22
8. Price RW, Brew BJ (1997) Central and peripheral nervous system complications. In: Curran J, Essex M, Fauci AS (eds) AIDS-etiology, diagnosis and prevention. Philadelphia, Lippincott-Raven, pp 331–353
9. Dore GJ, McDonald A, Li Y *et al* (2003) Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. AIDS 17: 1539–1545
10. Luft BJ, Hafner R, Korzun A *et al* (1993) Toxoplasmic encephalitis in patients with the Acquired Immunodeficiency Syndrome. N Engl J Med 329: 995–1000
11. Wallace MR, Rossetti RJ, Olsen PE (1993) Cats and toxoplasmosis risk in HIV-infected adults. JAMA 269: 76–77
12. Israelski DM, Chmiel JS, Poggensee L *et al* (1993) Prevalence of Toxoplasma infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. J Acquir Immune Defic Syndr Hum Retrovirol 6: 414–418
13. Ammassari A, Scoppettuolo G, Murri R *et al* (1998) Changing disease patterns in focal brain lesion-causing disorders in AIDS. J Acquir Immune Defic Syndr Hum Retrovirol 18: 265–371
14. Julander I, Martin C, Lappalainen M *et al* (2001) Polymerase chain reaction for diagnosis of cerebral toxoplasmosis in cerebrospinal fluid in HIV-positive patients. Scan J Infect Dis 33: 538–541
15. McFadden GI, Roos DS (1999) Apicomplexan plastids as drug targets. Trends Microbiol 7: 328–333
16. Mussini C, Pezzotti P, Goroni A *et al* (2000) Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type-1-infected patients: the changes in opportunistic prophylaxis study. J Infect Dis 181: 1635–1642
17. Weber T, Trebst C, Frye S *et al* (1997) Analysis of the systemic and intrathecal humoral immune response in progressive multifocal leukoencephalopathy. J Infect Dis 176: 250–254
18. Kitamura T, Aso Y, Kuniyoshi *et al* (1990) High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. J Infect Dis 161: 1128–1133
19. Sundsfjord A, Flaegstad T, Flo R *et al* (1994) BK and JC viruses in human immunodeficiency virus type 1-infected persons: prevalence, excretion, viremia, and viral regulatory regions. J Infect Dis 169: 485–490
20. Berger JR, Pall L, Lanska D *et al* (1998) Progressive multifocal leukoencephalopathy in patients with HIV infection. J Neurovirol 4: 59–68
21. Berger JR, Levy RM, Flomenholft D, Dobbs M (1998) Predictive factors for prolonged survival in acquired immunodeficiency syndrome – associated progressive multifocal leukoencephalopathy. Ann Neurol 44: 341–349
22. Fine HA, Mayer RJ (1993) Primary central nervous system lymphoma. Ann Intern Med 119: 1093–1104
23. Castagna A, Cinque P, d'Amico A *et al* (1997) Evaluation of contrast-enhancing brain lesions in AIDS patients by means of Epstein-Barr virus detection in cerebrospinal fluid and 201-thallium single photon emission tomography [letter]. AIDS 11: 1522–1523
24. Antinori A, De Rossi G, Ammassari A *et al* (1999) Value of combined approach with thallium-201 single photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. J Clin Oncol 17: 554–560
25. Skiest DJ, Crosby C (2003) Survival is prolonged by highly active antiretroviral therapy in AIDS patients with primary central nervous system lymphoma. AIDS 17: 1787–1793
26. Aboulafia DM (2002) Interleukin-2, ganciclovir, and high-dose zidovudine for the treatment of AIDS-associated primary central nervous system lymphoma. Clin Infect Dis 34: 1660–1662
27. Raez L, Cabral L, Cai JP *et al* (1999) Treatment of AIDS-related primary central nervous system lymphoma with zidovudine, ganciclovir, and interleukin 2. AIDS Res Hum Retroviruses 15: 713–719

Correspondence: Francisco Antunes, M.D., Ph.D., Clínica Universitária de Doenças Infecciosas, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, 1600 Lisboa, Portugal. e-mail: ip231874@ip.pt