REVIEW ARTICLE

HIV-2 and its neurological manifestations

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The human immunodeficiency virus type 2 (HIV-2) produces a similar spectrum of illness as HIV-1, including AIDS, and is clinically indistinguishable. There is evidence that it is less pathogenic, with a longer natural history. HIV-2 infection is endemic in West Africa, especially in the former Portuguese and French colonies. Trade, migration, war and tourism have been important factors in the spread of the virus through the subregion and beyond.

Diagnostic facilities necessary for the accurate diagnosis of neurological disease are not available in most of Africa and autopsy reports have been few. These constraints have restricted the information available on the pattern of neuropathology induced by HIV-2. However, it possesses neurotropic properties similar to those of HIV-1 and produces disease by means of direct action of the virus on the nervous system, and immunosuppression which allows opportunistic infections and tumours to occur.

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The human immunodeficiency virus type 2 (HIV-2) is the second human retrovirus that causes acquired immune deficiency syndrome (AIDS). It was first isolated in 1986 by Clavel *et al.*[1] from two West African patients with AIDS. This virus differed antigenically from HIV-1 and was originally called lymphadenopathy-associated virus type 2 (LAV-2). They also reported clinical and immunological data on 30 infected patients,[2] mostly from Guinea-Bissau, of whom 17 had AIDS. The new virus was isolated from the peripheral lymphocytes of 11 patients and shown to have cytopathic effects and reverse transcriptase activity. It had a similar tropism for CD4 T lymphocytes as HIV-1 but differed markedly in its envelope glycoprotein which appeared to be closely related to that of the simian immunodeficiency virus, the causative agent of an AIDS-like illness in captive macaques (SIV_{MAC}).[3]

HIV-2 infection is mainly confined to West Africa, especially the former Portuguese and French colonies; the virus has probably been circulating in the region since the 1960s.[4] Trade, migration, war and tourism have played important roles in its spread through the subregion and to other continents. There is a paucity of accurate information on the prevalence and distribution of infection in West African countries because of under-reporting and under-diagnosis of disease, and failure to use standardised methods in epidemiological studies. Nevertheless, significant levels of infection have been reported from Mali,[5] Senegal,[6] The Gambia,[7] Guinea-Bissau[8] and Ivory Coast[9] in a variety of sentinel groups. Infection outside West Africa has been reported but usually in patients connected with the region. The link with the former Portuguese colonies is provided by data on HIV-2 infection in Angola,[10,11] Mozambique[12] and Brazil.[13] In Europe significant numbers of patients have been reported from Portugal, France and Germany, including some cases where there was no West African association.[14]

HIV-2 is transmitted sexually,[14] by blood or blood products[15] and vertically from mother to child, in the same manner as HIV-1. There is some suggestion that perinatal transmission may be less efficient than in HIV-1.[16]

There were some early doubts about the pathogenicity of HIV-2 but it is now accepted that it produces a pattern of disease similar to that of HIV-1, including AIDS.[17] It may be less virulent, however, and have a longer natural history. This concept is supported by evidence of a long latent period in some patients[11,18,19] and by increasing age-specific prevalence rates in Guinea-Bissau.[16] A cross-sectional study of prostitutes in The Gambia showed that HIV-2-infected subjects had less abnormality of immunological parameters than those infected with HIV-1.[20] HIV-2 isolates show considerable antigenic variation with varying degrees of cytopathogenicity *in vitro*;[21] some strains exhibit little or no cytopathic effects.[22,23] It is possible that this may be important with regard to pathogenesis *in vivo*, but long-term prospective studies are required.

Clinical manifestations

Infection with HIV-1 or HIV-2 is not clinically distinguishable. Fevers, weight loss, chronic diarrhoea, lymphadenopathy, tuberculosis, Kaposi's sarcoma, prurigo and oral candidiasis are the main presenting features in Africa.

Neurotropism

The propensity of HIV-1 to attack the nervous system is well known[24,25] and there is now substantial evidence that HIV-2 exhibits a similar degree of neurotropism.

Brun-Vézinet and colleagues[26] in Paris isolated the virus from the cerebrospinal fluid (CSF) of 2 patients with AIDS or AIDS-related complex (ARC). Three patients had intrathecal production of IgG antibodies against HIV-2. Passive transfer from serum was excluded by the serum/CSF ratio of < 4; herpes simplex virus antibodies were also absent from the CSF despite the presence of high titres in serum.

Hugon *et al.*[27] reported a patient from Ivory Coast who presented in 1982 with a progressive spastic paraplegia. He had a normal myelogram and no neurological cause could be identified at that time. Four years later he was neurologically stable. HIV-2 antibodies were found by enzyme-linked immunosorbent assay and Western blot but HIV-1 and HTLV-1 antibodies were absent.

Klemm *et al.*[28] described a patient, seropositive for HIV-2, who developed incontinence, gait disturbance, cognitive

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disfunction and finally spastic paraplegia and peripheral neuropathy. He had cerebral atrophy on computed tomography (CT) and magnetic resonance imaging (MRI), with chronic inflammation and local production of immune globulins in the central nervous system.

Molecular biologists isolated a strain of HIV-2 from a Gambian patient dying solely of neurological disease.[29] This isolate produced higher levels of reverse transcriptase in fresh human monocytes/macrophages than in cultures of peripheral lymphocytes; it was suggested that this ability to invade macrophages was related to her neurological disease.

Thus HIV-2, in addition to two other human retroviruses (HIV-1 and HTLV-1), has neurotropic properties and the potential to cause neurological disease.

Neurological disease

Investigation of neurological symptoms in Africa is greatly hampered by the lack of sophisticated technological tools such as CT and MRI. There are few histopathological reports on post-mortem findings, and brain biopsies cannot be undertaken in the majority of countries in West Africa. Examination of the CSF usually only reveals nonspecific changes (raised protein levels, increased numbers of mononuclear cells). These constraints have severely restricted the information available from Africa and many patients with neurological disease probably remain unreported or undiagnosed. They form, however, a significant proportion of patients with HIV-2 AIDS or ARC; 11 (13%) of 82 patients who died in The Gambia over a 6-year period had neurological signs and symptoms (unpublished data).

The effects of HIV-2 on the nervous system may be the result either of the direct action of the virus itself, or the consequences of immunosuppression that lead to opportunistic infections and tumours.

Direct effects of HIV-2

The AIDS dementia complex is a constellation of cognitive, behavioural and motor abnormalities resulting from direct retroviral infection of the brain and spinal cord, and has been extensively reported in HIV-1 infection.[30]

The majority of patients reported with AIDS dementia complex due to HIV-2 have been investigated in Europe or America.[26,28,29] In an early report on retroviral disease in The Gambia,[31] 2 out of 11 patients who died of HIV-2 AIDS had dementia; post-mortem examination of 1 patient showed cerebral atrophy with dilated ventricles and nonspecific histological changes (D. C. W. Mabey — personal communication).

The only report on post-mortem findings in significant numbers of HIV-2 AIDS patients was by Lucas and colleagues.[32] Autopsy was performed on 28 (72%) of 39 dying seropositive patients in a general hospital and in a specialist neurology unit in Abidjan, Ivory Coast; 4 (14%) had giant cell encephalitis indicative of primary central nervous system involvement.

Aseptic meningitis[33] and myelopathy[34] may occur at the time of seroconversion in HIV-1 infections. The only report of a primary HIV-2 infection described a similar clinical illness.[35] The spastic paraplegia reported in a patient from Ivory Coast[27] may have represented a primary HIV-2 infection of the spinal cord.

Opportunistic infections and tumours

These arise as a consequence of the destruction of CD4 lymphocytes by the virus. In addition there is functional impairment of macrophages and natural killer cells leading to suppression of the immune surveillance system. New infections, especially fungal or viral, may lead to disease as a consequence of this loss of cell-mediated immunity, or there may be reactivation of a previous, latent infection.

The protozoon, *Toxoplasma gondii*, is the most important cause of opportunistic infection of the central nervous system. It produces cerebral abscesses, often multiple, which cause headaches, fits and focal neurological deficits such as ataxia, hemiplegia and dysphasia. Toxoplasma antibody levels are not a useful guide in diagnosis although they are rarely absent in the presence of active disease.[36] There is a typical appearance on CT, with ring-like contrast enhancement; toxoplasma encephalitis has been diagnosed in HIV-2-infected patients in Europe[11,26] and the USA.[37] In Africa cerebral toxoplasmosis was found on post-mortem in 4 (14%) patients in Abidjan[32] and in 1 patient in The Gambia.[31] Involvement of the basal ganglia may lead to movement disorders;[38] 1 patient in The Gambia with hemiballismus responded well to anti-toxoplasma therapy (P. T. Corrah — personal communication). A parkinsonian syndrome with tremor, cogwheel rigidity and dyskinesia has also been observed (C. M. Tang — personal communication); this patient had HIV-2 antibodies in the CSF and may have had direct involvement of the extrapyramidal system with the virus. *T. gondii* is a common cause of neurological disease in HIV-2 AIDS patients, and is frequently undiagnosed in Africa due to lack of facilities; it is also treatable, so a therapeutic trial of anti-toxoplasma drugs is warranted in all such patients.

Cryptococcal meningitis is an opportunistic fungal infection, the initial port of entry of which is the lungs. Patients with HIV-2 infection and cryptococcal meningitis have been described in The Gambia,[31] Ivory Coast[32] and the USA[37] but, surprisingly, it does not appear common; no such patients have been seen in The Gambia in the last 5 years (P. T. Corrah — personal communication).

Cerebral lymphoma is a rapidly fatal opportunistic B-cell tumour which requires CT and brain biopsy for diagnosis during life. It was present in 1 patient in the first reported series of HIV-2 AIDS patients in West Africa,[2] and in another at autopsy in Ivory Coast.[32]

Tuberculosis is the most important opportunistic infection in Africa, both for HIV-1 and HIV-2 infection.[9] Tuberculous meningitis, however, seems relatively uncommon although post-mortem studies suggest that it may be under-diagnosed.[39]

A history of herpes zoster has a strong positive predictive value (90%) for HIV-1 seropositivity[40] in Central Africa. No studies on HIV-2 infection and herpes zoster have been reported but this association appears weak in West Africa. This may be due to the low seroprevalence and reduced pathogenicity of HIV-2.

The natural history of neurosyphilis has been altered by HIV-1 infection with an accelerated clinical course, a

decreased latent period and an increased relapse rate.[41] There is no reported relationship between HIV-2 infection and neurosyphilis, which again may reflect a lesser degree of pathogenicity.

There is limited information on cytomegalovirus infection in HIV-2 disease. Post-mortem studies indicate that it does occur.[32] Progressive multifocal leuko-encephalopathy, caused by the JC virus, has not been reported. There is no association with cerebral malaria, which is mainly a disease of young children in West Africa, nor has HIV-2 infection been documented in patients with African trypanosomiasis.

Conclusions

The absence of hard data on the neuropathology of HIV-2 infection is due to its low prevalence worldwide, compared with HIV-1, together with the absence of diagnostic facilities in west Africa, which is the major endemic region. Nevertheless there is good evidence that it produces a similar pattern of disease to HIV-1, even if it is less pathogenic; it has neurotropic effects and causes disease by direct invasion of the nervous system and immunosuppression that allows opportunistic infections. South African patients with HIV-2 disease will probably at some time have lived in the former Portuguese colonies of Angola and Mozambique.[42]

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REFERENCES

1. Clavel F, Guetard D, Brun-Vézinet F, *et al.* Isolation of a new human retrovirus from West African patients with AIDS. *Science* 1986; **233:** 343-346.
2. Clavel F, Mansinho K, Chamaret S, *et al.* Human immunodeficiency virus type 2 infection associated with AIDS in West Africa. *N Engl J Med* 1987; **316:** 1180-1185.
3. Daniel MD, Letvin NL, King NW, *et al.* Isolation of a T-cell tropic HTLV-III-like retrovirus from macaques. *Science* 1985; **228:** 1201-1204.
4. Kawamura M, Yamazaki S, Ishikawa K, Kwofie TB, Tsujimoto H, Hayami M. HIV-2 in West Africa in 1966. *Lancet* 1989; **1:** 385.
5. Brun-Vézinet F, Peeters M, Guindo A, Maiga Y, Sangare A, OHFOM. HIV-1 and HIV-2 in Mali (Abstract 5018). Fourth International Conference on AIDS, Stockholm, 1988.
6. Kanki P, M'boup S, Marlink R, Siby T, Travers K, Essex M. Epidemiology and transmission of HIV-2 in Senegal (Abstract FC 658). Sixth International Conference on AIDS, San Francisco, 1990.
7. Wilkins A, Hayes R, Alonso P, *et al.* Risk factors for HIV-2 infection in The Gambia. *AIDS* 1991; **5:** 1127-1132.
8. Poulsen AG, Aaby P, Gottschau A, Dias F, Kvinesdal B, Molbak K. HIV-2 in Bissau, 1987-1989: prevalences and incidence in a sample of the general population (Abstract TRTG 6). Fifth International Conference on AIDS in Africa, Kinshasa, 1990.
9. De Cock KM, Gnaore E, Adjorlolo G, *et al.* Risk of tuberculosis in patients with HIV-1 and HIV-2 infections in Abidjan, Ivory Coast. *BMJ* 1991; **302:** 496-499.
10. Matos Almeida MJ, Santos Ferreira MO, Lourenco MH, Cohen T, Azevedo Pereira JM. HIV-1 and HIV-2 serological survey in Luando Norte, Northeastern province of Republica Popular de Angola (Abstract MGP 2). Fifth International Conference on AIDS, Montreal, 1989.
11. Saimot AG, Couland JP, Mechali D, *et al.* HIV-2/LAV-2 in Portuguese man with AIDS (Paris 1978) who had served in Angola in 1968-74. *Lancet* 1987; **1:** 688.
12. De la Cruz F, Barreto J, Palha de Sousa C, Barquet L. HIV in Mozambique. A general overview (Abstract ThGP 22). Fifth International Conference on AIDS, Montreal, 1989.
13. Veronesi R, Mazza CC, Santos Ferreira MO, Lourenco MH. HIV-2 in Brazil. *Lancet* 1987; **2:** 402.
14. De Cock KM, Brun Vézinet F. Epidemiology of HIV-2 infection. *AIDS* 1989; **3:** suppl 1, S89-S95.
15. Hughes A, Corrah T. Human immunodeficiency virus type 2 (HIV-2). *Blood Rev* 1990; **4:** 158-164.
16. Poulson AG, Kvinesdal B, Aaby P, *et al.* Prevalence and mortality from human immunodeficiency virus type 2 in Bissau, West Africa. *Lancet* 1989; **1:** 827-831.
17. De Cock KM, Brun Vézinet F, Soro B. HIV-1 and HIV-2 infections and AIDS in West Africa. *AIDS* 1991; **5:** suppl 1, S21-S28.
18. Ancelle R, Bletry O, Baglin AC, *et al.* Long incubation period for HIV-2 infection. *Lancet* 1987; **1:** 688-689.
19. Bryceson A, Tomkins A, Ridley D, *et al.* Long incubation period for HIV-2 AIDS. *Lancet* 1988; **2:** 221.
20. Pepin J, Morgan G, Dunn D, *et al.* HIV-2 induced immunosuppression among asymptomatic West African prostitutes: evidence that HIV-2 is pathogenic but less so than HIV-1. *AIDS* 1991; **5:** 1165-1172.
21. Schulz TF, Whitby D, Hoad JG, Corrah T, Whittle H, Weiss RA. Biologic and molecular variability of human immunodeficiency virus type 2 isolates from The Gambia. *J Virol* 1990; **64:** 5177-5182.
22. Evans LA, Moreau J, Odehouri K, *et al.* Characterisation of a non-cytopathic HIV-2 strain with unusual effects on CD4 expression. *Science* 1988; **240:** 1522-1524.
23. Kong LI, Lee SW, Kappers JC, *et al.* West African HIV-2-related human retrovirus with attenuated cytopathicity. *Science* 1988; **240:** 1525-1529.
24. Levy JA, Shimabukuro J, Hollander J, Mills J, Kaminsky L. Isolation of AIDS-associated retrovirus from cerebrospinal fluid and brain from patients with neurological symptoms. *Lancet* 1985; **2:** 586-588.
25. Goudsmit J, Wolters EC, Bakker M, *et al.* Intrathecal synthesis of antibodies to HTLV-III in patients without AIDS or AIDS related complex. *BMJ* 1986; **292:** 1231-1234.
26. Brun-Vézinet F, Rey MA, Katlama C, *et al.* Lymphadenopathy-associated virus type 2 in AIDS and AIDS-related complex. *Lancet* 1987; **1:** 128-132.
27. Hugon J, Giordano C, Dumas M, *et al.* HIV-2 antibodies in African with spastic paraplegia. *Lancet* 1988; **1:** 189.
28. Klemm E, Schneweis KE, Horn R, Tackmann W, Schulze G, Schneider J. HIV-2 infection with initial neurological manifestation. *J Neurol* 1988; **235:** 304-307.
29. Kuhnel H, von Briesen H, Dietrich U, *et al.* Molecular cloning of two West African human immunodeficiency virus type 2 isolates that replicate well in macrophages: a Gambian isolate from a patient with neurologic acquired immunodeficiency syndrome, and a highly divergent Ghanaian isolate. *Proc Natl Acad Sci USA* 1989; **86:** 2383-2387.
30. Brew BJ, Sidtis JJ, Rosenblum M, Price RW. AIDS dementia complex. *JR Coll Physicians Lond* 1988; **3:** 140-144.
31. Mabey DCW, Tedder RS, Hughes ASB, *et al.* Human retroviral infections in The Gambia: prevalence and clinical features. *BMJ* 1988; **296:** 83-86.
32. Lucas S, Hounnou A, Diomande M, *et al.* The pathology of terminal HIV-2 infection in Abidjan. Côte D'Ivoire (M.O. 102). Sixth International Conference on AIDS in Africa, Dakar, 1991.
33. Cooper DA, Gold J, MacLean P, *et al.* Acute AIDS retrovirus infection — definition of a clinical illness associated with seroconversion. *Lancet* 1985; **1:** 537-540.
34. Denning DW, Anderson J, Rudge P, Smith H. Acute myelopathy associated with primary infection with human immunodeficiency virus. *BMJ* 1987; **294:** 143-144.
35. Besnier JM, Barin F, Baillou A, Liard F, Choutet P, Goudeau A. Symptomatic HIV-2 primary infection. *Lancet* 1990; **1:** 798.
36. Pinching AJ. Neurological aspects of the acquired immune deficiency syndrome. *JR Coll Physicians Lond* 1988; **3:** 136-139.
37. Kloser PC, Mangia AJ, Leonard J, *et al.* HIV-2-associated AIDS in the United States. The first case. *Arch Intern Med* 1989; **149:** 1875-1877.
38. Nath A, Jankovic J, Pettigrew LC. Movement disorders and AIDS. *Neurology* 1987; **37:** 37-41.
39. Lucas SB, Ochida M, Wabinga H. The pathology of severe morbidity and mortality caused by HIV infection in Africa. *AIDS* 1991; **5:** suppl 1, S143-S148.
40. Colebunders RL, Mann JM, Francis H, *et al.* Herpes zoster and HIV infection in Africa. *J Infect Dis* 1988; **157:** 314-318.
41. Johns DR, Tierney M, Felsentein D. Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. *N Engl J Med* 1987; **316:** 1569-1572.
42. Lyons SF, Clausen L, Schoub BD. HIV-2-induced AIDS in Southern Africa. *AIDS* 1988; **2:** 406-407.

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