Neurological aspects of the acquired immune deficiency syndrome

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Patients with the acquired immune deficiency syndrome (AIDS) constantly challenge the clinician with the diversity not only of the secondary opportunistic infections that may be seen, but also of the ways in which they may present. In the nervous system, the range of opportunistic events is slightly less wide than for other sites, but each may present with clinical features which, though varying greatly from patient to patient, can be remarkably similar to one another. The situation is made more difficult by the occurrence of HIV encephalopathy (AIDS dementia complex), which always enters the differential diagnosis of neurological presentations in AIDS, is as diverse in its presentations as are the opportunistic diseases, has many clinical features in common with them and for which there are no simple pathognomonic tests.

At present, there is no definitive treatment for HIV encephalopathy apart from possible benefits of zidovudine (AZT) in some patients. On the other hand, most of the opportunistic disorders are eminently treatable. Furthermore, HIV encephalopathy not uncommonly coexists with neurological opportunistic infection. For these reasons, HIV encephalopathy must be regarded by the clinician as a diagnosis of exclusion, only to be considered as probable when systematic investigation of neurological symptoms has failed to reveal an opportunistic infection or indeed any other possible cause of neurological disorder. This systematic approach must also include repeated re-evaluation of the patient over time, in case features of early opportunistic infection have been overlooked or in case an opportunistic event supervenes in a patient with established encephalopathy. This article concentrates on the clinical aspects of neurological opportunistic disease against the background of HIV encephalopathy described in greater detail by B. J. Brew and colleagues elsewhere in this series of articles.

The pattern of neurological disease in AIDS

There are two major determinants of the pattern of opportunistic disease seen in AIDS. Firstly, the nature of the immune deficiency which predominantly affects cell-mediated immunity as a result of the elimination and functional impairment of CD4 (T4) lymphocytes and associated macrophage and natural killer cell functional defects. Secondly, the relative frequency of different disorders is determined by the background prevalence of the opportunistic organisms in the person or population affected; this will vary in different geographical areas, age groups and risk behaviours. Several of the infections and tumours are the result of latent infection with the causative organism established many years previously, so that previous exposure, for example during travel to other geographical areas, may have to be taken into account.

In our experience of over 200 patients with AIDS at St Mary’s Hospital, London, Toxoplasma gondii cerebral abscesses occurred, in 10 per cent of cases, Cryptococcal meningitis in 5 per cent, cerebral lymphoma in 2 per cent and progressive multifocal leucoencephalopathy in 1 per cent. Cytomegalovirus (CMV) retinitis affected some 10 per cent of patients but CMV encephalitis seemed less common, affecting perhaps 2 per cent. We have not yet seen mycobacterial infection of the nervous system although this has been reported, with tuberculomas due to M. tuberculosis, and with tuberculous meningitis. Kaposi’s sarcoma affecting the central nervous system is extremely rare.

In about 25 per cent of AIDS cases the virus itself is responsible for overt clinical evidence of encephalopathy by the end of their course, and it is usually only pronounced in advanced disease. We have seen three cases of HIV encephalopathy in patients without full-blown AIDS over the same period, two of whom had AIDS-related complex. Peripheral neuropathy, usually presenting with a symmetrical glove and stocking distribution but sometimes as mononeuritis multiplex, affected some 10 per cent, in many cases associated with evidence of autonomic neuropathy. Myelopathy was seen in 2 per cent of cases, usually in association with other neurological features and we have seen one instance of a disorder resembling amyotrophic lateral sclerosis. A painful myopathy with wasting occurred in 2 per cent of cases.

Diagnostic approaches to neurological presentations in AIDS

The development of symptoms of CNS disease in AIDS or AIDS-related complex (ARC) patients should be investigated immediately with CT brain scan, to exclude space-occupying lesions such as toxoplasma abscesses and cerebral lymphoma and diffuse processes with characteristic scan appearances, such as progressive multifocal leucoencephalopathy. IV contrast must always be used to

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demonstrate enhancement, which is usually, though not universally, present in toxoplasmosis and cerebral lymphoma. Even if cerebral atrophy is seen, which may indicate the presence of relatively advanced HIV encephalopathy, lumbar puncture must follow. Cerebrospinal fluid (CSF) should be examined microscopically and by culture, especially for cryptococcus and mycobacteria, and by sensitive antigen detection techniques for *Cryptococcus neoformans*. Serum cryptococcal antigen should also be sought.

Magnetic resonance imaging (MRI) scanning may be more sensitive in the early detection of toxoplasma lesions and may also show patchy changes reflecting HIV encephalopathy; however, MRI scanning may not be readily available and its diagnostic role is not yet firmly established. Serial CT scanning may give equally useful information. Electroencephalography and psychometric testing are valuable adjuncts in patients with suspected seizures or cognitive impairment respectively.

Toxoplasma antibody testing has a limited diagnostic role since the B cell abnormalities seen in AIDS with polyclonal hypergammaglobulinemia, make a rise in titre uncommon and unreliable as a diagnostic tool. However, a baseline toxoplasma antibody level on AIDS diagnosis to detect evidence of prior infection, is helpful in assessing the later development of a space-occupying lesion, as toxoplasmosis is rare in AIDS patients who are seronegative. Recent studies have indicated that evidence of intrathecal synthesis of toxoplasma antibodies can be a useful diagnostic tool. If a space-occupying lesion or lesions are seen, especially in a toxoplasma seropositive patient, empirical therapy with sulphadiazine/pyrimethamine or dapsone/pyrimethamine should be given for two weeks, with follow-up clinical examination and CT brain scan. In the event of a failure to respond or where there is a strong initial suspicion of an alternative diagnosis, brain biopsy of accessible lesions is indicated to exclude cerebral lymphoma or other less common lesions.

All patients with AIDS and ARC must have regular fundoscopic examination to detect early CMV retinitis, which may initially be symptomless if it affects the peripheral fields. While this commonly occurs in isolation, it is sometimes part of disseminated CMV infection which may include a subacute encephalopathy. Culture of buffy coat cells and CSF for CMV are useful diagnostic tools in suspected disseminated or CNS infection. Uveitis and vitreous floaters are sometimes found in association with CMV retinitis. Toxoplasma retinitis is also occasionally seen.

When these approaches do not yield a diagnosis, metabolic causes of encephalopathy and subclinical epilepsy must be excluded. Care should also be taken to exclude psychosis and the effects of psychotropic drugs, to which patients with AIDS and HIV infection seem unduly sensitive, probably due to subclinical or overt HIV encephalopathy. If no space-occupying or other characteristic scan lesion or meningeal infection can be demonstrated, a provisional diagnosis of HIV encephalopathy can be made, whether or not there is evidence of cerebral atrophy. Neuropsychometric studies may show characteristic deficits. The diagnostic value of evoked potential studies in HIV encephalopathy is currently under evaluation.

Peripheral nerve lesions may be assessed by nerve conduction studies and biopsy where appropriate. Tests of autonomic function such as Valsalva response on ECG and postural hypotension may be helpful, although the latter is also a feature of Addison’s disease which can occur in AIDS due to CMV or tuberculous adrenalitis. Electromyography and biopsy may be performed in myopathy but do not show characteristic features in most cases; creatine phosphokinase levels are not usually raised.

**Features and treatment of neurological disease in AIDS**

Toxoplasma cerebral abscesses are usually multiple. They may present with non-specific features of headache, fever (usually slight), confusion, fits and/or central ataxia or there may be focal symptoms and signs, such as hemiplegia, dysphasia, hemianopia or unilateral cerebellar ataxia. Frontal lesions may present with higher function abnormalities or pseudocerebellar ataxia. Raised intracranial pressure is rarely evident. Symptoms generally develop over days or weeks, although acute presentations do occur. The typical CT scan appearances are of multiple low attenuation areas, occasionally resembling infarcts. These show irregular ring-enhancement, except in very early cases, and are surrounded by large areas of low attenuation (oedema or encephalitis).

Treatment with intravenous sulphasalazine and pyrimethamine leads to clinical and radiological improvement over one to two weeks. Patients who have allergic reactions to sulphonamides, which are unduly common in AIDS, may be successfully treated with dapsone/pyrimethamine. Folic acid supplementation is essential. There is no consistent benefit from the treatment of cerebral oedema with mannitol or a short course of dexamethasone in the acute phase. Therapy is continued for two to four weeks, depending on clinical response and thereafter maintenance therapy with sulphadoxine/pyrimethamine (Fansidar) thrice weekly for life is necessary to prevent recurrence. Some patients may develop focal epilepsy after recovery. Fits are readily controlled with sodium valproate or carbamazepine.

Cerebral lymphoma may occur in isolation or may be part of more widespread disease. The presentations are exactly similar to those seen in toxoplasmosis although the lesions on CT scanning are typically single. Treatment with radiotherapy may produce some benefit but the overall prognosis is poor.

Cryptococcal meningitis may present as a pyrexia alone and features of meningitis may be minimal or absent due to the impaired immune response. Headache, central ataxia or confusion are commonly present, but focal signs are unusual. Fits are uncommon at presentation but may occur following successful treatment, as may secondary hydrocephalus. CSF usually contains few cells; although cryptococci are usually seen, they may be missed in some patients, the diagnosis only being established by the presence of CSF and serum cryptococcal
antigen or on culture (which should be prolonged, since some organisms seem to be very slow growing).

Treatment hitherto has been with four to six weeks of intravenous amphotericin (0.6 mg/kg from day 2) and 5-flucytosine, but according to early reports oral fluconazole (a trial drug) seems to be effective. Without maintenance therapy, relapse is common, usually after several months. Maintenance schedules currently being used are intermittent intravenous amphotericin (once every one to four weeks), but fluconazole looks an attractive and apparently effective alternative.

Cytomegalovirus retinitis may or may not present with scotoma, but on fundoscopy shows characteristic chorioretinitis with haemorrhages. Cotton wool spots must be distinguished, as these do not always indicate CMV retinitis although they are commonly associated with it. The encephalopathy associated with disseminated CMV infection is typically subacute with diffuse features, fever, confusion and ataxia. Treatment of CMV infection is with ganciclovir (DHGP), a trial drug available on compassionate basis, or with Foscarnet, also a trial drug but, of lower efficacy. Maintenance therapy is always required for retinitis since relapse is common. The effect of treatment is the cessation of active retinitis with loss of haemorrhages and healing of chorioiditis, but there is little if any recovery of vision in affected sites, emphasising the importance of early diagnosis and maintenance therapy. Late retinal detachment can occur in patients with extensive disease.

Progressive multifocal leucoencephalopathy tends to present with the insidious development of cognitive dysfunction associated with some motor signs, usually pyramidal and cerebellar. CT scan shows a characteristic appearance of patchy change in white matter. No effective treatment is available.

HIV encephalopathy (AIDS dementia complex) is discussed elsewhere in this issue. It is notable that its clinical features are of a generally slow development of progressive cognitive impairment, with defects in short-term memory and concentration, mood change with depression or frontal features and central ataxia. Fits may occur. Later, psychomotor retardation and withdrawal may develop with more pronounced motor features, pyramidal, extrapyramidal and cerebellar, incontinence and frank dementia. Notable sensitivity to and bizarre reactions following psychotropic drugs may be seen, resembling those seen in children, the elderly and patients with presenile dementia. A more rapid development of encephalopathy may occur, especially in patients with intercurrent infections. CT scan may show diffuse cerebral atrophy and lesions may be evident on MRI scanning, particularly in subcortical sites, but normal appearances may be seen with either. Myelopathy seems less common and is usually present in association with cerebral changes. Peripheral neuropathy is frequently painful with dysesthesiae, which may precede overt sensory loss, and is often associated with some evidence of autonomic neuropathy. There is evidence of both demyelination and axonal loss on nerve conduction studies. Symptomatic treatment with analgesics, carbemazepine, sympathetic block or transcutaneous nerve stimulation have only had modest success.

Zidovudine (AZT) has led to apparent improvement in encephalopathy and possibly peripheral neuropathy in some patients with established disease, although the benefits are partial and seem restricted to patients with more rapidly developing disease. This indicates that a reversible element is due to functional neuronal impairment from HIV infection of microglia and macrophages, whether induced by viral or macrophage products, whereas the irreversible and more slowly developing disease reflects true neuronal loss. We have also seen that zidovudine dose-reduction, especially in those patients with prior encephalopathy, may lead to an acute, generally transient, meningoencephalitis that resembles the acute encephalitis which occurs in association with acute HIV disease at the time of seroconversion. This probably reflects a rebound in viral replication and has important implications for the use of this drug. Whether or not zidovudine can prevent the development of HIV encephalopathy or neuropathy when used earlier in the course of infection has yet to be determined, but is obviously a possibility of considerable potential impact. Our early studies indicate that it can improve previously impaired neuropsychometric parameters in patients without overt neurological disease. (A polymyositis-like disorder, with wasting of proximal muscles and raised CPK, has been described in patients on long-term zidovudine and is being seen increasingly.)

Conclusions

Neurological presentations in AIDS are common, though protein and non-specific. Patients must be rigorously assessed so that opportunistic infection may be promptly diagnosed and effectively treated. The impact of HIV encephalopathy, a diagnosis of exclusion in patients with HIV infection, is considerable and options for treating or preventing this with the use of zidovudine and other antiretroviral agents have yet to be fully clarified.

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Further Reading

1. Asher, D, Epstein L. and Goudsmit, J. (1987) Human immunodeficiency virus in the central nervous system. In Current topics in AIDS, (Eds M.S. Gottlieb et al.) Vol. 1. Chichester: John Wiley.
2. Forster, S. M. and Pinching, A.J. (1987) Acquired immune deficiency syndrome and its neurological complications. In Recent advances in neurology (Ed C. Kennard) Vol. 5. Edinburgh: Churchill Livingstone.
3. Helbert, M., Robinson, D., Gor, D. et al. (In press) Acute meningoencephalitic illness seen in patients with AIDS on zidovudine dose-reduction.
4. Navia, B. A., Petitio, C.K., Gold, J. W. M., et al (1986) Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome. Annals of Neurology, 19, 224-238.
5. Navia, B. A. and Price, R. W. (1986) Central and peripheral nervous system complications of AIDS. In AIDS and HIV infection. (Ed A. J. Pinching). London: Saunders.
6. Potaszman, I, Resnick, L., Luft, B. J. and Remington, J. S. (1988) Intrathecal production of antibodies against Toxoplasma gondii in patients with toxoplastic encephalitis and the acquired immune deficiency syndrome. Annals of Internal Medicine, 108, 49.
Lupus: early history of the wolf

But in our own flesh though we bear diseases
Which have their names only ta’en from beasts
As the most ulcerous wolf and swinish meal

said Bosola in The Duchess of Malfi (1613–14). Later in the 17th century, when cancer had come to mean malignant growth, he might have continued: Or scirrhous crab that grips till dread decease.

Surely he was right to wonder, why call a disease ‘wolf’ or ‘lupus’? It is not just verbalism, both the animal and disease are al-dhi’b in Arabic; lupus vulgaris is dhi’bah [1]. In 1590 Burrough [2] wrote of lupus as a ‘malignant ulcer quickly consuming the nether parts; and it is very hungry like unto a wolf.’

In classical Greek or Latin, lupus signifies a wolf, but not the disease. Connection with lupe, Greek for pain or sad plight, has been suggested by Skinner [3] but is ruled out by unambiguous animal reference, and so is lippus, Latin for blue-eyed. Lupinus was the plant lupin to Horace and Pliny.

The modern meaning. Lupus erythematosus is the form most often seen in Britain now. Its definition is attributed to Cazenave [4] who described superficial lupus which attacks the face and neck. In 1876 Squire [5] spoke of ‘so-called lupus erythematosus, or sebaceous lupus or bat’s wing disease.’

According to Bateman [6], who set down the views of his deceased colleague Willan, the term lupus was intended by Dr Willan to comprise, together with a noli me tangere affecting nose and lips, other slow tubercular affections, especially about the face, commonly ending in ragged ulcerations of the cheeks, forehead, eyelids and lips, and sometimes appearing in other parts of the body, where they gradually destroy the skin and muscular parts to a considerable depth.’

This was the original description of lupus vulgaris, the name chosen by Willan. Previously lupus was a different disease.

Lupus 1300–1800. James’s medical dictionary [7] was published in 1745. The entry under lupus ends: ‘A cancer is, also, sometimes called Lupus because it eats away the flesh.’ Burrough’s description [2] of 1590 is quoted above; Blancard’s dictionary [8], originally published in the same era, says ‘Lupus signifies a malignant cancerous Ulcer, seizing on the lower parts, especially of the thighs, and eating away the Flesh around it like a Wolf that preys on all it meets’—although not usually man, according to a modern author [9]. John Halle [10] mentioned cancers which ‘may shewe lyke a Lupine, and sometime growth

3’-azido-3’ deoxythymidine. Lancet, i, 132.

9. Zuger, A., Louie, E., Holsman, R. S. et al. (1986) Cryptococcal disease in patients with the acquired immune deficiency syndrome. Annals of Internal Medicine, 104, 234.