

AIDS dementia complex

BRUCE J. BREW, MB, FRACP*, JOHN J. SIDTIS, PhD*,
MARC ROSENBLUM, MD**, RICHARD W. PRICE, MD*

*Departments of *Neurology and **Pathology
Memorial Sloan-Kettering Cancer Center, New York*

Infection by the human immunodeficiency virus type 1 (HIV-1), and particularly its terminal phase, the acquired immunodeficiency syndrome (AIDS), is frequently complicated by neurological dysfunction. This may relate to a variety of secondary complications resulting from immunodeficiency, including opportunistic infections (for example, cerebral toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy) or neoplasms (primary and secondary brain lymphomas) [1,2]. The brain of the HIV-1 infected patient is also vulnerable to the effects of systemic disease and organ dysfunction including metabolic encephalopathies and vascular or haematological disorders. However, even more common than these secondary afflictions is a central nervous system (CNS) syndrome, the AIDS dementia complex which is unique to individuals infected with HIV-1 and appears, at least in part, to result from direct brain infection by this retrovirus.

In this article we briefly consider the clinical features of the AIDS dementia complex, aspects of its neuropathology, virology and viral pathogenesis, problems of diagnosis and the prospects for treatment. More detailed reviews of this syndrome and of the neurological complications of HIV-1 infection and AIDS are available elsewhere [3].

Clinical features of the AIDS dementia complex

The AIDS dementia complex can be classified as one of the subcortical dementias. Although the notion of a subcortical dementia has not been universally accepted [4], the essential features of this classification have been slowed mentation, forgetfulness, personality change, and apathy, without more focal deficits of aphasia, apraxia, amnesia, or neglect. This classification has been applied to the intellectual changes associated with a number of diseases with significant subcortical pathology including progressive supranuclear palsy, Parkinson's Disease, and Huntington's Disease [5-7]. The classification of the AIDS dementia complex as a subcortical dementia is consistent with neuropathological findings in afflicted patients, with the results of studies localising the viral infection, as well as its clinical manifestations. Clinically,

the AIDS dementia complex is characterised by a distinct constellation of cognitive, motor and behavioural abnormalities, and while there is variation in the temporal evolution of dysfunction in these three domains, there is sufficient constancy to define a syndrome.

Complaints of difficulty with concentration, forgetfulness and slowing in mental agility are among the initial symptoms of cognitive impairment [8]. These may be confused with the symptoms accompanying general fatigue, depression or even anxiety, but as they begin to intrude upon work performance and capacity for activities of daily living, it becomes clear that their severity is disproportionate to the level of medical disease or dysphoria. At this early stage, routine mental status examination may yield only mild abnormality and may, indeed, appear to be within the normal range. Neuropsychological testing using appropriate instruments, particularly tests which incorporate timed performance, are more often sensitive to the condition [9]. Subsequently, as the disorder progresses, diffuse cognitive deficit becomes evident and affects nearly all spheres of cognition, although evidence of 'focal' cognitive abnormalities such as aphasia or apraxia is characteristically absent. In most patients, judgement and insight also appear to be relatively preserved until late in the disease, although this socially important aspect of the condition has not yet been studied carefully. In those who undergo the most severe progression, the end stage is a condition of near or absolute mutism with incapacity for all but the most rudimentary social or intellectual interaction.

Complaints of motor impairment often lag behind those pertaining to cognition, but when present most commonly relate to clumsiness in walking, weakness or fatigue of the legs, and, less frequently, impairment in manual dexterity [8]. More commonly, evidence of motor dysfunction is detected on examination before the onset of symptoms and includes slowed ocular saccades or interrupted smooth pursuits and slowness of rapid alternating movements of the extremities. Abnormal reflexes are also relatively common and include both generalised hyperactivity most conveniently judged by assessing the jaw jerk and with the appearance of pathological reflexes, the most common of which is the snout response. In progressive disease, lower extremity dysfunction most often then evolves from ataxia to paraparesis. Urinary and faecal incontinence also intervene later in the disease and complicate management. In patients with pathological

Address for correspondence: Dr Richard W. Price, Department of Neurology, Memorial Hospital, 1275 York Ave., New York, NY 10021, USA.

evidence of vacuolar myelopathy (see below), the motor deficit often predominates over cognitive dysfunction, and there may be relative preservation of mentation as a spastic-ataxic gait evolves. In such patients the major abnormalities are those of slowness of gait, clumsiness of leg movements, ataxia and eventual weakness. Reflexes may be hyperactive; however, these patients often exhibit a concomitant peripheral neuropathy which may confuse localisation. Despite pathological changes in the posterior columns of the spinal cord, clinical examination of these patients usually reveals relative sparing of sensation in the absence of peripheral neuropathy.

Behavioural abnormalities commonly accompany both the cognitive and motor deficit and are characterised by a parallel slowing of initiative, drive and sociability [8]. Patients may appear to undergo a personality change with loss of their usual energy and 'sparkle'. They may appear apathetic with loss of interest both in work and in social intercourse. While this is often misconstrued as depression, dysphoria is surprisingly uncommon. As with intellectual and motor dysfunction, progression of this apathy evolves into terminal indifference to surroundings. An interesting and as yet poorly characterised subgroup of patients may exhibit a more agitated state with hyperactivity and, at times, frank mania or delirium [10,11].

Neuropathology, virology and viral pathogenesis

The neuropathological substrate of the AIDS dementia complex has only been partially clarified and there remain several important questions regarding the spectrum of abnormalities and their significance. Likewise, while studies from a number of laboratories using several complimentary techniques have demonstrated the presence of HIV-1 infection in brain, the interpretation of these findings is still unsettled. The field is now at a point where clear questions need to be formulated and addressed.

One can consider the neuropathology of the AIDS dementia complex as consisting of overlapping neuropathological 'sets' [12,13]. Whether these represent a spectrum of the variable expression of one disease process or whether, alternatively, they reflect distinct aetiopathogenic processes remains to be determined. This pathological diversity is one of the major reasons to retain the term AIDS dementia complex as a *syndrome* rather than as a disease entity. The three neuropathological sets include multinucleated cell encephalitis, diffuse white matter pallor, and vacuolar myelopathy.

Multinucleated cell encephalitis

In perhaps 20-40 per cent of autopsied AIDS patients [12-15], histopathological examination reveals a distinct abnormality which is virtually pathognomonic of HIV infection. This consists of combined infiltration of multinucleated cells and macrophages with a variable lymphocytic and microglial accompaniment. Frequently associated with these reactive infiltrates are microscopic foci of tissue rarefaction. This multinucleated-cell en-

cephalitis is characteristically noted in a subgroup of patients with the most severe clinical form of the AIDS dementia complex.

It is in these patients with multinucleated cells that virological studies have conclusively demonstrated the presence of HIV-1 in brain. In these, Southern Blot hybridisation has detected the presence of proviral DNA, *in situ* hybridisation has similarly revealed both proviral DNA and viral RNA, immunohistochemistry has detected viral antigens, and electron microscopy has visualised virions. Infection demonstrated by these various techniques appears to be confined largely or exclusively to the multinucleated cells, macrophages and microglia. In fact, it is very likely that the multinucleated cells result from virus-induced cell fusion and thus are the *in vivo* counterpart of the characteristic *in vitro* cytopathology manifest as syncytium formation.

With the focus of infection being confined largely, if not exclusively, to cells of monocyte/macrophage and microglial origin, a major question is how such infection injures the brain causing the profound dysfunction noted in many of these patients. Additionally, in a number of these patients infection is quite limited to a small number of cells with a restricted anatomical distribution. Why then is there global dementia? These considerations and the absence of discernible destruction of neurones, oligodendrocytes or astrocytes in most cases, have led investigators to consider whether indirect mechanisms of injury of these intrinsic cellular elements may be important [16].

Diffuse white matter pallor

More common than multinucleated cell encephalitis is a diffuse involvement of the white matter with generalised pallor often accompanied by astrocytic proliferation and sometimes vacuolation [12-15, 17]. This type of abnormality is present in varying degree in nearly all AIDS patients. It is most notable in those with more severe disease and progressively less marked in those with milder clinical dysfunction. Since it can also be seen in patients without clinical dysfunction, and because there are no unique features to distinguish this abnormality, its specificity and significance may be questioned. While the degree of pallor may parallel clinical severity, precise quantitative correlation has not yet been evaluated. In those patients with pallor in the absence of multinucleated cell and macrophage infiltrates, the presence of HIV-1 in the brain is usually not found by current nucleic acid or antigen detection techniques, and it therefore cannot be stated with certainty that this abnormality is caused by direct brain infection. Additionally, as with the multinucleated cell encephalitis in some patients, the clinical severity of neurological dysfunction appears to exceed the magnitude of the pathological abnormality.

Vacuolar myelopathy

Although multinucleated cell infiltrates may extend into the spinal cord, a more common finding is a vacuolar myelopathy with prominent involvement of the posterior and lateral columns, histopathologically very similar to

that of subacute combined degeneration related to vitamin B12 deficiency [18]. These patients often suffer dementia in addition to myelopathic symptoms. While its prevalence is somewhat higher in those with multinucleated-cell encephalitis, it clearly can occur in patients without the multinucleated cell changes [13,19]. In fact, the vacuolar change and multinucleated cell encephalitis may well represent independent processes. Additionally, the geographic prevalence of vacuolar myelopathy appears to be variable [20,21]. Virological studies thus far have not directly implicated HIV-1 in the genesis of the vacuolar change. While HIV-1 can be cultured from spinal cords with these pathological changes [22,23], clear localisation of the virus to regions of vacuolation or to the oligodendrocytes which form and maintain the myelin sheaths has not been demonstrated. Thus, at the present time neither the aetiology nor pathogenesis of this pathological component of the AIDS dementia complex can be regarded as established.

Some general issues of pathogenesis

The pathological diversity in patients with the AIDS dementia complex and the fact that HIV-1 has only clearly been correlated with the multinucleated cell encephalitis raise a number of questions regarding both the aetiology and pathogenesis of HIV-1 infection and its clinical expression. Does HIV-1 cause the entire spectrum of the AIDS dementia complex or is this syndrome the result of several processes with convergent effects on brain function?

The AIDS dementia complex also needs to be considered in the context of the evolution of HIV-1 CNS infection which includes the relatively unusual incidence of acute meningoencephalitis and aseptic meningitis and the perhaps more frequent occurrence of asymptomatic infection [3,22,24]. During the acute stage of HIV-1 infection a small number of patients may manifest an acute encephalitis or meningitis. However, many, if not the majority, of infected individuals exhibit evidence of previous and, in some instances, perhaps chronic asymptomatic HIV-1 infection in the cerebrospinal fluid (CSF). Later in the course of infection certain patients then develop aseptic meningitis [25] or the AIDS dementia complex. What determines the evolution of these events and their variability among patients? We have argued elsewhere that progressive immunosuppression, and particularly depressed immune defences against HIV-1, may have an important 'permissive influence' on the development of the AIDS dementia complex and progressive HIV-1 brain infection [16]. However, immunosuppression alone does not provide a full explanation for the variability in the development of the AIDS dementia complex, and the emergence of particular strains or variants of HIV-1 with enhanced neurotropism or neurovirulence may be a second important factor [26,27]. Such variations in the virus may also account for the spectrum of neuropathological changes discussed earlier. It can be speculated that some variants may cause productive brain infection with multinucleated cell encephalitis, others may cause the diffuse pallor, and still others may induce

vacuolation. Clearly further work is needed to explore these possibilities.

An additional salient question relates to the targeting of particular areas of the brain. For each of the pathological 'sets' outlined above, major involvement concentrates in subcortical structures, including most notably the basal ganglia and central white matter but also the brainstem and spinal cord. As with other selective vulnerabilities, there is a need to explain this regional distribution.

As noted earlier, the degree of clinical dysfunction in some cases exceeds what would be expected from the limited extent of pathological abnormalities. There may be mild, moderate or even severe AIDS dementia complex without frank demyelination or neuronal loss, at least as appreciated by routine histopathological assessment [19]. These considerations have led investigators to focus on the role of indirect mechanisms of injury involving release of toxic virus- or cell-coded products by infected cells [16,28].

Epidemiology and natural history

The epidemiology and natural history of the AIDS dementia complex have yet to be clearly defined. Characterisation of the syndrome and estimates of its prevalence and natural history are based largely, indeed almost exclusively, on observations made with clinically afflicted patients. Such observations are helpful in providing first approximations and in formulating hypotheses, but their narrow viewpoint has severe limitations. Only recently are the results of population-based studies becoming available.

On the other hand, clinical observations make it clear that the AIDS dementia complex can be an important source of morbidity in the late stages of HIV-1 infection. Our clinical experience suggests that over 60 per cent of patients dying with AIDS have exhibited antemortem symptoms and signs of the AIDS dementia complex [8], and more recent analysis of patients in the late stages of disease suggests an additional 25 per cent of patients with subclinical or mild disease. However, earlier in the course of infection the prevalence is clearly lower. Perhaps as many as 25 per cent of individuals may have symptomatic disease before or at the time of presentation with systemic AIDS and again perhaps another 25 per cent exhibit mild or subclinical abnormalities at this stage [8]. Recognition of early development of neurological disease has led to inclusion of the AIDS dementia complex within the revised CDC criteria [29]. It is, however, important to emphasise that those patients who present with the AIDS dementia complex often have 'preAIDS' symptoms or signs such as oral thrush, herpes zoster, weight loss, malaise, fatigue, fever or other constitutional abnormalities [30].

It is our impression that the prevalence of overt AIDS dementia complex and even of subclinical abnormality in individuals who are otherwise asymptomatic, with or without simple adenopathy, with normal or nearly normal immunity (assessed by T4 lymphocyte counts and functional studies) is very low. Since the medical and social implications of prevalence of early AIDS dementia

complex are potentially substantial, this issue needs careful study.

Diagnosis

While formal criteria for diagnosis have not been established, the overall nature of the AIDS dementia complex is now sufficiently clear to allow recognition in most cases. It is important to emphasise that this is a *clinical diagnosis* and that one cannot simply screen patients and establish a final diagnosis based solely on a battery of neuropsychological tests or radiographic findings.

The diagnosis of AIDS dementia complex can be considered as consisting of several components which are usually evaluated concomitantly. Potential susceptibility to the disorder is evaluated by testing for the presence of systemic HIV-1 infection and usually relies on serology. Staging of immunosuppression is also helpful in estimating the probability of AIDS dementia complex and is based on the history of systemic complications and on laboratory assessment of immunosuppression, the most convenient measure of which is the T4 lymphocyte subset count. While in most patients the presence of HIV-1 infection is well known before a diagnostic evaluation, the potential widening scope of the epidemic may lead to increasing numbers of cryptic cases.

An initial step in neurological evaluation involves exclusion of other CNS disorders. In patients with very mild disease, the most troublesome differential diagnostic issues relate to whether symptoms are due to psychiatric disease, in particular depression or anxiety, or to the fatigue and malaise of systemic illness. When neurological symptoms and signs are more severe, differential diagnosis then centres on opportunistic infections or neoplasms.

Finally, diagnosis requires the presence of the characteristic clinical symptoms and signs enumerated above and discussed in more detail elsewhere [3]. As noted earlier, neuropsychological testing may be of ancillary help in diagnosis but is principally useful as a research tool, allowing serial quantitative measurement of impairment. Although not diagnostically specific and subject to the confounding influence of 'practice effect', neuropsychological test performance provides a useful means of following changes in patient status for natural history and therapeutic studies. Such tests can be used for epidemiological studies but their results should always be interpreted within a clinical context. In individuals with limited judgement or insight or those who deny their illness, neuropsychological testing may also provide objective evidence of impairment but must be interpreted in the context of the wide normal range.

Prospects for therapy

Individual case reports and anecdotal experience suggest that zidovudine (AZT) may favourably influence the symptomatology of the AIDS dementia complex [31]. However, well-documented observations are limited, and further studies are needed to evaluate more carefully the frequency of therapeutic response, the magnitude of such

a response and the long-term outcome of treatment. Certainly, AZT is not the ideal therapy. It is our individual experience that patients may progress with respect to the AIDS dementia complex while on treatment, but more often therapeutic failure relates to patients' inability to tolerate AZT on a long-term basis and the resultant abandonment of antiviral therapy.

Acknowledgements

Our own studies of the AIDS dementia complex have been supported by PHS grants NS-19048 and NS-25701, New York State AIDS Institute grant AR-074, the Life and Health Insurance Medical Research Fund, and the Rudin Foundation. We thank Ms Francine Kaskel for preparation of the manuscript.

This article is based on a paper delivered at a Conference on Neuropsychiatric Disease and AIDS held at the Royal College of Physicians of London in October 1987.

References

1. Snider, W. D., Simpson, D. M., Nielsen, S. *et al.* (1983) *Annals of Neurology*, **14**, 403.
2. Levy, R. L., Bredesen, D. E. and Rosenblum, M. L. (1985) *Journal of Neurosurgery*, **62**, 475.
3. Brew, B., Sidtis, J., Petito, C. K. and Price, R. W. (In press) In *Advances in Contemporary Neurology* (Ed F. Plum) Philadelphia: F. A. Davis Co.
4. Whitehouse, P. J. (1986) *Annals of Neurology*, **19**, 1.
5. Albert, M. L., Feldman, R. G. and Willis, A. L. (1974) *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 121.
6. Cummings, J. L. and Benson, D. F. (1984) *Archives of Neurology*, **41**, 874.
7. Joynt, R. J. and Shoulson, I. (1985) In *Clinical Neuropsychology*, (Ed K. M. Heilman and E. Valenstein) pp 453-479. New York: Oxford University Press.
8. Navia, B. A., Jordan, B. D. and Price, R. W. (1986) *Annals of Neurology*, **19**, 517.
9. Tross, S., Price, R. W., Navia, B. *et al.* *AIDS* (In press).
10. Rundell, J. R., Wise, M. G. and Ursano, R. J. (1986) *American Journal of Psychiatry*, **143**, 777.
11. Kleihues, P., Lang, W., Burger, P. C. *et al.* (1985) *Acta Neuropathologica (Berlin)*, **68**, 333.
12. Budka, H., Costanzi, G., Cristina, S. *et al.* (1987) *Acta Neuropathologica (Berlin)*, **75**, 185.
13. Navia, B. A., Cho, E. S., Petito, C. K. and Price, R. W. (1986) *Annals of Neurology*, **19**, 525.
14. De La Monte, S. M., Ho, D. D., Schooley, R. T., Hirsch, M. S. and Richardson, E. P. (1987) *Neurology*, **37**, 562.
15. Petito, C. K., Cho, E. S., Lemann, W., Navia, B. A. and Price, R. W. (1986) *Journal of Neuropathology and Experimental Neurology*, **45**, 635.
16. Price, R. W., Brew, B., Sidtis, J. *et al.* (1988) *Science*, **239**, 586.
17. Rhodes, R. H. (1987) *Human Pathology*, **18**, 636.
18. Petito, C. K., Navia, B. A., Cho, E. S. *et al.* (1985) *New England Journal of Medicine*, **312**, 874.
19. Price, R. W., Sidtis, J. and Rosenblum, M. (1988) *Annals of Neurology*, **23**(suppl), 27.
20. Vinters, H. V. (1987) *Annals of Neurology*, **21**, 612.
21. Vazeux, R., Brousse, N., Jarry, A. *et al.* (1987) *American Journal of Pathology*, **126**, 403.
22. Ho, D. D., Rota, T. R., Schooley, R. T. *et al.* (1985) *New England Journal of Medicine*, **313**, 1493.
23. Rosenblum, M. L., Levy, R. M. and Bredesen, D. E. (1988) In *AIDS and the nervous system*. New York: Raven Press.
24. Carne, C. A., Smith, A., Elkington, S. G. *et al.* (1985) *Lancet*, **ii**, 1206.
25. Hollander, H. and Stringari, S. (1987) *American Journal of Medicine*, **83**, 813.

26. Anand, R. (1988) *Annals of Neurology*, 23(suppl), S66.
27. Cheng-Mayer, C. and Levy, J. A. (1988) *Annals of Neurology*, 23(suppl), S58.
28. Ratner, L., Polmar, S. H., Paul, N. and Ruddle, N. (1987) *AIDS Research and Human Retroviruses*, 3, 147.
29. Centers for Disease Control (1987) *Morbidity and Mortality Weekly Report*, 36, 1S.
30. Navia, B. A. and Price, R. W. (1987) *Archives of Neurology*, 44, 65.
31. Yarchoan, R., Thomas, R. V., Grafman, J. et al. (1988) *Annals of Neurology*, 23(suppl), S82.

Hieronymus Fracastorius 1483–1553

The name Fracastorius may be known to readers for his medical poem *Syphilis sive Morbus Gallicus* which was printed in Verona in 1530 and is reputed to have given the name Syphilis to the disease. Few readers however may be aware of the other achievements of this remarkable Italian polymath.

Fracastorius, born in Verona in 1483, studied medicine at the University of Padua. He practised in Verona and built up a reputation not only in Italy but also throughout Europe. He had many other interests including physics, astronomy, mathematics, geology, botany and philosophy.

At the time Fracastorius was practising medicine, a new sexually transmitted disease was spreading throughout Europe whose most obvious symptom was pustules breaking out over the whole body leaving the sufferer disfigured. This so-called 'love-pestilence' began to attract Fracastorius' attention, and in order to describe and explain the illness, Fracastorius turned to classical literature and mythology. Legend has it that a herdsman committed sacrilege by disobeying the sun-god and erecting temples to the king Alcithous. The god in his anger struck down the whole population with this 'pestilence'. The name of this herdsman was not known to Fracastorius and so he turned to the classics, in this case, Ovid's story of Sipylus, the second son of Niobe. Niobe herself lived on the mountain Sipylus, having been turned into

stone by Zeus following the slaughter of her fourteen children by Artemis and Apollo. Fracastorius used a certain amount of poetic licence to convert the name from Sipylus to Syphilis and in 1530 wrote the poem relating the legend of the shepherd Siphylus: *Siphylis sive Morbus Gallicus*. This poem became so famous that the word syphilis became the universal term for the so-called 'French disease' or 'love pestilence'.

The poem was translated into English by Nahum Tate, an English poet and playwright probably best remembered today for his hymn *While shepherds watched*. A copy of his *Poetical history of the French disease* published in 1685 may be seen in the British Museum.

Fracastorius, in addition to being a physician and a poet, made important contributions in the field of bacteriology. In 1546, he published a *Treatise on contagion* where he described three modes of transmission of an infection: by direct contact; by fomites; and thirdly 'at a distance' by which he meant particles not perceived by the senses (*seminaria contagionum*), a remarkable feat considering that bacteria were an unknown entity at that time and for many years to come. In addition he can be credited with the first clear account of typhus fever.

Fracastorius died in 1553 of apoplexy. Six years later a statue was erected in his memory at Verona.

A. K. BANERJEE
St Helen's Hospital, Hastings, Sussex