Human immunodeficiency virus-associated neurobehavioural disorder

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Acquired immunodeficiency syndrome (AIDS) is increasingly becoming recognised as a disease of the central nervous system (CNS) as well as a disorder in cell mediated immunity. It appears that 75-80 per cent of patients with AIDS will develop evidence of brain pathology [1]. This pathology has been variously termed HIV encephalitis and HIV encephalopathy. Changes at post-mortem examination include reduced brain weight with enlargement of the sulci and ventricles, myelin pallor in the white matter, infiltration of white matter with macrophages and lymphocytes, presence of multinucleated giant cells and glial nodules, and focal areas of demyelination and neuronal loss [1-3].

The cause of brain pathology in AIDS is still not known. It is thought that HIV-1 is principally responsible, though in many cases myelin pallor, typically found in the centrum semiovale, occurs in the absence of demonstrable virus in the brain. Whether this represents insensitivity of our current methods, or whether virus might be present in the brain, replicating itself at a very low level, producing metabolic toxins, and yet escaping observation, cannot be answered at present. When virus has been demonstrated, it has tended to be located principally in the basal ganglia and subcortical white matter [2]. HIV has not been convincingly demonstrated to infect neurones themselves, and it is speculated that the virus may enter the brain in macrophages. It is possible that toxic products or other physiological disturbances produced by such infected macrophages, or perhaps infected glial cells, can contribute to brain dysfunction [2,3].

The clinical correlate of HIV encephalopathy has been termed the AIDS dementia complex [4]. Its early clinical manifestations include a subjective sense of slowing, difficulties with learning and remembering, motor incoordination, especially of the lower extremities, and a tendency toward apathy. Later signs include most of the well known features of a dementing disorder, including severe memory loss, problems with reasoning, slowing of verbal fluency, disorientation, and various disturbances of behaviour. The latter can range from severe apathy and extreme withdrawal to occasional cases of agitation, manic excitement, and frank psychosis reminiscent of paranoid schizophrenia.

The natural history of neuropsychiatric disorder in HIV infection remains poorly understood. Clinical experience suggests that the more severe forms of AIDS-associated dementia occur in the most advanced forms of disease; nevertheless, AIDS dementia complex can sometimes be an early presenting sign [5] and we have seen cases in which a florid psychiatric presentation, such as paranoid features and hallucinations, may be the initial major signs of underlying AIDS [6].

Our recent work has focused on the possibility that brain involvement can occur relatively early in the course of HIV infection, perhaps before major symptoms of immunodeficiency become evident. To explore this possibility we have been conducting neuropsychological, psychiatric, and nuclear magnetic resonance (NMR) brain-imaging studies with groups of homosexual men at varying stages of HIV disease.

Study 1: Neuropsychological findings at various stages of HIV infection

Our first study, recently published elsewhere [7], examined 55 homosexual men divided into four groups. They were relatively well educated. Their average age in the four groups ranged from 33 to 39, and they had from two to four years of university study. Group A were 15 men meeting Center for Diseases Control (CDC) criteria for AIDS. Group B were 13 men meeting CDC criteria for AIDS-related complex (ARC). Group C consisted of 16 homosexual men who were HIV antibody positive (HIV+) but who were either completely asymptomatic,
or whose medical symptoms were sufficiently mild that they could not be classified as having ARC or AIDS. Finally, in Group D were 11 homosexual men who were HIV antibody negative (HIV−), but whose histories included engaging in sexual activities which were thought to place persons at risk for HIV infection. None of these subjects were abusers of intravenous drugs nor had they been recipients of blood products. Further, none of the subjects, on routine clinical neurological examination, had signs or symptoms suggestive of neurologic disease or AIDS dementia complex at the time of the initial neuropsychological study.

**Method**

We chose a set of neuropsychological tests which we thought would provide reasonably broad coverage of different cognitive abilities, yet be economical of time. The testing included:

(a) a measure of verbal intelligence (the Vocabulary Test of the Wechsler Adult Intelligence Scale—WAIS-R);
(b) the WAIS-R digit span as a measure of simple attention;
(c) Halstead’s Category Test to reflect abstracting ability;
(d) the Trail-Making Test, parts A and B as measures of speed of information processing and cognitive flexibility;
(e) story and figure learning and recall from the Wechsler Memory Scale (WMS) to determine efficiency of learning and remembering; and
(f) the Paced Auditory Serial Addition Test (PASAT) as an index of speeded information processing [7].

**Table 1.** Criteria for classifying individual neuropsychological test performance as ‘probably’ or ‘definitely’ impaired

| Test Type                        | Probable | Definite |
|----------------------------------|----------|----------|
| Digit span (scaled score)        | 6-7      | 0-5      |
| Story learning (number of trials to reach criterion) | 3        | 4,5      |
| Story recall (% loss after 1 h)  | 25-30    | >30      |
| Figure learning (number of trials to reach criterion) | 3        | 4,5      |
| Figure recall (% loss after 1 h) | 25-30    | >30      |
| Category errors                  | 50-60    | >60      |
| Symbol-digit paired associate learning (total in four trials) | 16-21    | <16      |
| Paced auditory serial addition test (number correct in first trial) | 25-35    | <25      |
| Trails B time, sec               | 85-99    | >99      |

*A subject’s overall neuropsychological performance was abnormal if either at least one test score was definitely impaired or at least two test scores were probably impaired.

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**Results of neuropsychological testing**

The performance of all subjects was classified as either ‘unimpaired’ or ‘impaired’ using the decision rules shown in Table 1. Because some of the neuropsychological tests yield several measures, we selected only nine of these as the critical ones, the selection being based on the wish to achieve a broad sampling of various cognitive functions, but without unnecessary duplication. For a subject’s overall performance to be considered impaired, it was necessary for him to achieve either one definitely impaired score in one of the nine critical measures, or at least two probably impaired scores.

The results are presented in Fig. 1. The proportion of persons classified as impaired rises from 9 per cent in the HIV− group to 87 per cent in the AIDS group. Of particular interest, but requiring replication, is the finding that 44 per cent of HIV+ individuals who were either asymptomatic, or whose symptoms were not of sufficient magnitude to be classified AIDS or ARC, fell into the impaired range on these tests.

Impairment occurred most frequently in the Category Test, a sensitive measure of novel problem solving (abstracting ability). For example, definitely or probably impaired performance was registered by 8 of 15 AIDS patients, 5 of 13 ARC patients, and 4 of HIV+ persons on this test alone, but no HIV− participant showed impairment in this test.

Another common source of impairment in the AIDS patients was the measure of speeded information processing—the PASAT. Thirteen of 15 AIDS patients performed in the probably or definitely impaired range on that test, compared with 4 of 13 with ARC, 4 of 16 who were HIV+, and 1 of 11 HIV− patients.

Probable or definite impairment on one or other of the memory tests was noted in 9 of 15 AIDS patients, 4 of 13 with ARC, 4 of 16 who were HIV+, and 2 of 11 who were HIV−. We did not find any evidence that verbal or visual memory was disproportionately affected in those who had difficulties. When memory defects were noted, they were typically in the process of learning new infor-
mation, although some patients also had difficulties in longer-term retrieval of previously learned verbal and visual information.

Nuclear magnetic resonance brain-imaging (NMR)

Because this first study was a pilot endeavour and therefore not well funded, we had to restrict NMR examinations to the two groups in which we had reason to expect increased rates of abnormalities. Therefore, scans were limited to 13 patients diagnosed as having AIDS and to 10 with ARC.

NMR method

A General Electric Signa 1.5 tesla system was used. To obtain some images with relative proton density weighting and others with relative T2 weighting, we used an asymmetric two echo pulse sequence with a repetition time of 2000 msec and echo times of 25 and 75 msec. Slices 5 mm thick were obtained at 7.5 mm intervals. The field of view (FOV) was set at 24 cm with a 256 x 256 matrix and two excitations. As many slices as possible were obtained in the axial plane. These were normally supplemented by coronal sections using the same pulse sequence as well as T1 weighted (TR = 600 msec, TE = 25 msec) sagital scans.

Results of NMR scanning

A neuroradiologist (JRH) who was kept blinded to group membership, used a predetermined protocol to rate general patterns of abnormality, location of lesions, degree of ventricular or sulcal enlargement, symmetry, and an overall impression.

Nine of 13 AIDS patients and 5 of 10 ARC patients were classified as having NMR abnormality; 8 of the 23 scans revealed sulcal or ventricular enlargement, and 10 had parenchymal lesions consisting either of multiple areas of high signal intensity or, in four of the AIDS patients, larger and more confluent areas of abnormality, principally in the white matter, suggestive of encephalitis. Figs 2-5, provide some examples of these NMR abnormalities.

Summary of study 1

In summary, the pilot study provided preliminary information that there could be cognitive impairment, generally mild in nature, even in HIV+ persons who were relatively asymptomatic from a medical standpoint. The rate of abnormality in neuropsychological functioning appears to increase among people with more advanced forms of HIV disease, until virtually all of the AIDS patients have at least mild neuropsychological deficit. The commonest cognitive difficulties revolve around novel problem solving, learning and remembering, and speed of information processing.

NMR brain scans, performed in the AIDS and ARC groups only, revealed that a high proportion of AIDS patients had either 'brain shrinkage', parenchymal lesions, or combinations of these. Half of the ARC patients also had NMR abnormalities, though these were generally less extensive than those in the AIDS patients. For example, none of the ARC patients had the larger confluent areas of high signal which suggest diffuse white matter disease.

What is the natural history of HIV-associated brain change?

The incidence of HIV-associated organic mental disorder at various stages of the disease remains unknown. Similarly, the rate of progression of neuropsychiatric disorder, once the earliest signs of cognitive dysfunction have appeared, is also unknown. The onset of actual dementia is a poor prognostic sign, and many AIDS patients who develop frank dementia can be expected to die within a few months of onset of marked mental deterioration [5].

What about patients who evidence some neuropsychological disturbance, or may have some evidence of brain disease on the NMR, but are not severely symptomatic? The several case studies which follow serve to illustrate some of the variability we have observed.

Case A: rapidly progressing organic mental disorder

This 41-year-old single man received the diagnosis of AIDS after a bout of Pneumocystis carinii pneumonia. While in hospital, he was noted to be somewhat forgetful and mentally slowed, but there were no gross neurological signs. He responded well to a course of cotrimoxazole and was discharged home.

Approximately six weeks later, still in stable health, he underwent neuropsychological testing and an NMR brain scan (Table 2). His scores on Vocabulary and Digit Span indicate a man of average intelligence who was not having any difficulty with simple attention. Most of his other test results were grossly abnormal, however. For example, he made a large number of errors on the Category Test (impaired abstraction), had great difficulties learning a short story or simple geometric figures, and was also impaired on a task of associative learning. He was quite slow on effortful tasks that had a speeded component (eg PASAT, Trail Making, Digit Symbol), but his fluency (FAS test), though diminished, was not as impaired as some of the other functions described above.

In summary, although at a clinical level his neuropsychiatric signs were rather mild, formalised testing revealed generalised moderate to severe cognitive dysfunction.

The NMR brain scan (Fig. 2), accomplished at about the same time, provides a basis for understanding this generalised neuropsychological impairment. There are multiple areas of increased signal intensity within the white matter of both cerebral hemispheres; the right hemisphere is involved more than the left, and this lesion has somewhat more poorly defined margins. The picture is consistent with white matter encephalitis, although the responsible organism can only be guessed at.

This man died four months after the testing and scanning were completed. He developed a rapidly evolving AIDS dementia complex characterised by progressive
Table 2. Neuropsychological test results of cases presented.

|                  | Case A |         | Case B |         | Case C |         | Case D |         |
|------------------|--------|---------|--------|---------|--------|---------|--------|---------|
|                  | Initial| Follow-up| Initial| Follow-up| Initial| Follow-up| Initial| Follow-up|
| WAIS-R vocabulary| 11     | 14      | 15     | 10      | 10     | 15      | 16     |
| Digit span       | 12     | 12      | 12     | 10      | 11     | 15      | 19     |
| Digit symbol     | 6      | 8       | 7      | 9       | 13     | 10      | 12     |
| Category Test    | 104    | 79      | 91     | 80      | 60     | 9       | 5      |
| Trail Making B   | 300    | 83      | 74     | 139     | 62     | 50      | 37     |
| Tactual Performance Test (total time) | —   | 10.4    | 10.6   | 11.5    | 9.4    | 11.6    | 10.0 |
| Tapping Test*    | (78) 52| (80) 54 | (66) 44| (67) 45 | (77) 52| (67) 45 | (70) 47|
| Story learning (No. of trials) | >5 | 2       | 2      | 5       | 2      | 1       | 2      |
| Story recall (% loss) | 100 | 0       | 0      | 25      | 29     | 4       | 5      |
| Figure learning  | >5     | 1       | 1      | 1       | 1      | 1       | 1      |
| Figure recall (% loss) | 36  | 5       | 0      | 0       | 0      | 0       | 0      |
| Selective reminding—best of 6 trials | 5 | 12      | 8      | 10      | 9      | 11      | 12     |
| Symbol digit PAL | 2      | 28      | 28     | 16      | 18     | 28      | 28     |
| PASAT (No. correct—trial 1) | 13 | 30      | 40     | 26      | 46     | 10      | 49     |
| FAS              | 19     | 45      | 37     | 30      | 37     | 34      | 40     |

*In the AZT trial a non-standard time of 15 sec was used. The values in parentheses are the actual taps in 15 sec; the other values are the estimated scores for a 10 sec (standard) trial, obtained by multiplying the 15 sec value by 0.67.

amnesia, retardation, and disorientation. A painful bilateral sensory motor neuropathy complicated the last months of his life. He became bedfast, stuporous, and incontinent. He died from multiple infections approximately six months after initial diagnosis of AIDS.

This case illustrates the rapid progression toward death which has been observed by Navia and associates [5] in patients who became frankly demented. The interesting feature was that neuropsychological testing and NMR scanning picked up the severity of brain involvement about a month before the evolution of gross neuropsychiatric signs.

Case B: slow progression of subclinical brain disease followed by stabilisation

This patient was 35 years old when he was diagnosed as having AIDS, also following a bout of Pneumocystis pneumonia. Four months after an uneventful recovery from the pneumonia he underwent neuropsychological testing and an NMR brain scan prior to being included into a randomly controlled clinical trial of azidothymidine-zidovudine (AZT). Initial neuropsychological testing (Table 2) showed a man of above average intelligence who had normal motor speed on the tapping test and good fluency. At the same time, his initial testing revealed some disturbance of abstracting ability (Category Test errors = 79), some slowing in speed of information processing (PASAT) and an atypical score on the Digit Symbol Test (also reflecting slight psychomotor slowing). The initial NMR brain scan was unremarkable except for a few tiny areas of high signal intensity scattered in the white matter (these are not visible in the photographs, Fig. 3 (a) and (b).

Six months later, neuropsychological testing revealed a similar pattern of mild deficits, with some worsening of performance on the Category Test, on Digit symbol, and one of the memory tests (Selective Reminding). Concurrent NMR examination revealed a large irregular area of high signal intensity in the left frontal white matter as well as smaller scattered lesions bilaterally (Fig. 3 (c) and (d)).

Fig. 2. Case A: Multiple confluent areas of high signal, most prominent in the white matter of the right hemisphere. (From Grant et al. [1987] Annals of Internal Medicine, 107, 833. Copyright American College of Physicians. Reprinted with permission.)

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Fig. 3. Case B: (a) and (b) NMR brain scans are unremarkable on initial examination; (c) and (d) Six months later there is a large irregular area of high signal in the left frontal white matter, as well as smaller scattered lesions bilaterally.
Fig. 4. Case C: (a) and (b) Initial scans show lesions in both basal ganglia, with particular involvement on the left; (c) and (d) Six months later the lesions in (a) and (b) have cleared. Coincidentally, Case C was receiving zidovudine (AZT).
This individual, who happened to be in the placebo arm of the study, was administered open-label AZT at four months when the study was halted. Approximately one year after initial testing, he was medically stable, and showed no progression of neurological signs. His neuropsychological testing indicated some improvement. Six months later he developed CMV retinitus and another bout of Pneumocystis pneumonia. He became clinically demented with signs of confusion, thought disorganisation and periodic mutism. He had advanced dementia when he died 20 months after initial evaluation.

These observations suggest that neuropsychological testing may be able to identify cognitive deficits in HIV infected persons before obvious lesions can be detected on NMR scanning. Worsening of neuropsychological performance after six months was accompanied by major changes in NMR. It is possible that the underlying brain pathology simply had not advanced far enough at time of initial scanning for it to be visualised, although some functional (psychological test) impairment was already evident. The fact that this individual did not progress immediately to develop frank AIDS dementia complex suggests that the AIDS-associated neuropsychiatric syndrome need not progress inexorably, but might stabilise for considerable periods of time. Nevertheless, the early test results appeared to predict ultimate dementia.

Case C: clearing of NMR—partial improvement in neuropsychometry

This man was 39 years old when he was diagnosed as having AIDS. Prior to being randomly allocated to AZT treatment he underwent neuropsychological testing and NMR brain scanning. His clinical neurological examination at this time was remarkable only for some slowing in saccadic eye movements. He had no other abnormal neurological findings.

Initial neuropsychological testing revealed a man of average intelligence who did not have any particular difficulties concentrating. He had impaired problem solving ability (Category Test), difficulty with associative learning (Symbol Digit Paired Associate Learning Test), and his rate of information processing was slowed (PA-SAT). He was also slowed on a test that combined psychomotor speed and cognitive flexibility (Trail Making part B).

His NMR brain scan is shown in Fig. 4 (a) and (b). There are lesions in both basal ganglia and internal capsules, with particular involvement on the left side.

After six months of AZT, this individual registered some improvement in his neuropsychological performance, especially on tests involving psychomotor speed. However, two tests of memory, and one of abstracting ability remained abnormal.

In contrast, the NMR brain scans taken six months later showed complete clearing of lesions from the basal ganglia (Fig. 4 (c) and (d)). These results emphasize that brain lesions in HIV infection do not represent static phenomena; rather, they can undergo remarkable change, even complete clearing, as in this case. Whether the clearing was the result of treatment with AZT, or simply coincidental, remains to be seen.

While the neuropsychological testing showed some improvement, it was not to the extent that the NMR clearing might indicate. It seems possible, therefore, that some underlying metabolic abnormality of the brain was still present, though not capable of being visualised on NMR. Neuropsychological testing at 12 months indicated further improvement, though minor abnormalities persisted. This patient moved away from the city, but telephone contact was made at 23 months, a few days before he died of medical complications. While seeming slow and fatigued, he was not grossly demented insofar as could be determined by telephone.

Case D: occult NMR lesions without corresponding functional impairment

This man developed diarrhoea and cytomegalovirus (CMV) retinopathy at age 39. He was diagnosed as having AIDS and received neuropsychological testing and NMR brain scanning prior to inclusion in the randomly controlled AZT trial.

Both his initial and six-month follow-up neuropsychological testing were entirely unremarkable (Table 2). A bright man intellectually, he scored very well on tests of abstract reasoning, psychomotor speed, and memory.

The initial NMR brain scan showed small, bilaterally distributed areas of high signal intensity in the white matter of the frontal lobes (arrows, Fig. 5 (a) and (b)). He also had a mild increase in sulcal width (Fig. 5 (b) and (d)).

After six months of AZT treatment several of these small lesions had disappeared (Fig. 5 (c) and (d)). Once again, it cannot be said with certainty whether the AZT was causally related to regression of these lesions. It is evident from this case, however, that small lesions apparent on NMR scanning can be associated with entirely normal, even superior neuropsychological test performance, and lack of clinical neurological signs.

At 12 months, case D had developed neuropathy and neuropsychological testing revealed some psychomotor slowing, although his abstracting ability remained excellent. Because of leukopenia zidovudine was discontinued. He died without any evidence of intellectual decline at 16 months.

Effect of AZT on brain disease

Individual cases of remarkable improvement in mental status and even in NMR imaged brain pathology after a course of AZT have been reported. Indeed, Case C, described above, is an example of just such an association. Nevertheless, it remains an open question whether there is a systematic benefit in terms of central nervous system pathology in patients receiving AZT. A large multicentre clinical trial of AZT which involved patients with AIDS and ARC (not specifically selected for having neurological symptoms) has reported differentially better performance on the Trail Making Test among those who received the active treatment after a 16 week period [8].

We have had an opportunity to examine only a limited
number of patients on AZT and placebo as part of this same multicentre trial. Our own data do not suggest a systematic benefit from AZT on any of the tests we administered. As an example, Fig. 6 illustrates the mean scores on Trail Making part B (the test reported to show benefit in the above-mentioned study) of patients who received AZT ($n = 13$) and those who were on placebo ($n = 8$) at prerandomisation and at two, four and six months postrandomisation. It will be seen that both groups improve (ie take less time) as they are re-examined. This ‘practice effect’ is to be expected on repeated neuropsychological tests. At the same time, there does not seem to be any evidence that the slopes of the imaginary lines which could be drawn through the data points for controls and AZT treated groups are any different.

In summary, the present state of knowledge does not
permit any confident assertions about the role of AZT in reversing the HIV associated organic mental disorder. A multicentre trial is under way in the USA studying the effects of AZT in HIV infected persons with neurological symptoms. At the conclusion of this study, it should be clearer what role, if any, AZT has in the management of the neurological complications of HIV disease.

Summary and conclusions

AIDS, ARC, and other HIV-associated diseases were originally conceptualised exclusively in terms of defects in cell-mediated immunity and its consequences. But it is now becoming clear that HIV disease can also be a primary neuropsychiatric disorder, although the precise mechanism by which the retrovirus causes impairment in brain function and, ultimately, structural brain damage, remains obscure.

The work presented here indicates another shift in our thinking concerning HIV infection. Until recently it was believed that neurological and neuropsychiatric phenomena tended to occur in the late stages of HIV disease. While that might be true for the more severe form of symptomatology that has been termed the AIDS dementia complex, we believe there is at least preliminary evidence that cognitive change can occur earlier in the course of illness, perhaps even in some medically asymptomatic HIV+ individuals.

Other investigators have also noted increased neuropsychological abnormality in patients before they developed AIDS or ARC. For example, Janssen et al. [9] found that about half their patients with lymphadenopathy syndrome (LAS) had some neuropsychological test deficits. Duara et al. [10] recently reported on cerebral metabolic rates for glucose in seven HIV+ asymptomatic individuals, compared to 10 HIV+ controls. Four of the HIV+ individuals had abnormal asymmetry in frontal and temporal regions suggesting focal reduction in cerebral glucose metabolism. Further indirect evidence that virus can enter the central nervous system early in the course of HIV disease comes from the work of McArthur and associates [11]. These investigators attempted to grow HIV from the cerebrospinal fluid of 16 HIV+ men who had neuropsychiatric symptoms (none had AIDS and only one had ARC) and seven HIV+ men who were completely asymptomatic. Virus was isolated from the CSF of 11 of the 16 HIV+ neuropsychiatrically symptomatic men and two of the seven who were completely asymptomatic. Although based on very small samples, the finding that HIV can be cultured from the CSF of even completely asymptomatic individuals suggests that virus might enter the central nervous system at a very early stage. Research currently in progress should help us to determine whether presence of virus in the CSF correlates with neuropsychometry, MRI, or PET studies.

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