

EDITORIAL

The evolution of neurobehavioural complications of HIV infection¹

Changes in mood, behaviour, and neurocognitive functioning can accompany infection by Type 1 Human Immunodeficiency Virus (HIV-1), the causative agent of acquired immune deficiency syndrome (AIDS). Some of these neurobehavioural phenomena reflect attempts to cope with and adapt to knowledge and complications related to a devastating, fatal illness. Others reflect the impact of biological factors on brain function. Elsewhere we have suggested the use of the terms 'psychogenic' and 'neurogenic' to allude to these two broad categories of causation of behavioural disorders (Grant & Atkinson, 1990).

The neuropsychiatric disturbances that can accompany HIV infection tend to evolve in concert with the natural history of the underlying medical disorder. Fig. 1 presents the idealized relationship of the key processes – underlying deterioration of cell mediated immunity (represented by declining CD4+ lymphocyte numbers), progress of medical symptomatology, mood disturbance, and appearance of neurocognitive disturbance. In general, it can be seen that the 'psychogenic' phenomena (i.e. anxiety, depression, coping difficulties) tend to be most in evidence during transition points in the illness – at the time of discovery of serostatus, during appearance of medical symptoms, and as part of the transition into more serious stages of disease. Disturbance in cognitive function, thought to reflect progress of brain disease, has a low prevalence during the medically asymptomatic phase, with substantial increase during later phases of the illness.

PSYCHOPATHOLOGY IN 'AT RISK' GROUPS

Before considering neurobehavioural complications of HIV infection it is necessary to understand that, in the Western context, the two major groups which have been at risk for becoming infected with HIV – homosexual men and intravenous drug-users – can also carry with them elevated risk of psychological difficulties which may precede (and, possibly contribute to) becoming infected. Failing to grasp this, we can make the error of ascribing to HIV infection and its consequences, behavioural disorders which might have little to do with the infection *per se*. For example, research conducted with multiple drug-abusers before HIV came on the scene has demonstrated that the majority can be classified as having personality disorders, including antisocial personality, passive/aggressive or passive/dependent personality, and mixed personality disorders. Structured personality inventories such as the Minnesota Multiphasic Personality Inventory (MMPI) demonstrate elevations in scales 4 and 9 (often linked with antisocial traits), and, in many cases, scales, 2, 7, and 8, indicative of depression, anxiety, low self-esteem, and 'ego boundary' disturbances (Lachar *et al.* 1978).

With regard to the homosexual risk group, recent data comparing lifetime prevalence of diagnosable psychiatric disorders between seronegative gay men and heterosexual men matched for age and social position indicate that there is substantially more syndromal pathology in the homosexuals compared to the heterosexuals. For example, Atkinson *et al.* (1989) found that the lifetime prevalence of major depression in a group of seronegative homosexual men was 31% compared to 9% in heterosexual men. The figure for the heterosexual group was comparable to estimates of lifetime prevalence for major depression derived from large epidemiological catchment area studies (5% – Robins *et al.* 1984). Atkinson *et al.* (1989) also found that the lifetime prevalence of anxiety disorders (39%) greatly exceeded that reported among heterosexual men.

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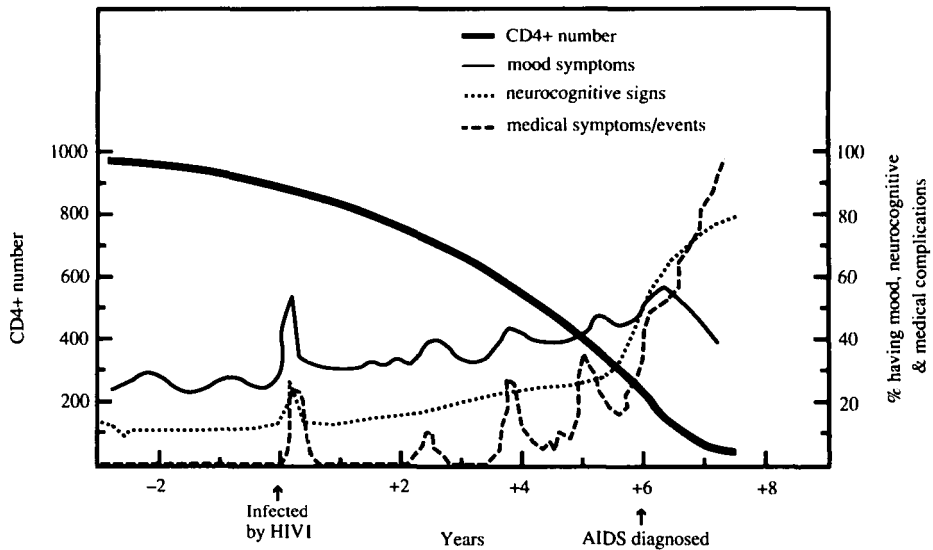


FIG. 1. Progress of medical and neurobehavioural events in HIV-1 infection.

Jacobsberg *et al.* (1989) also reported an elevated lifetime prevalence of mood disorder (43 %) and personality disorder (27 %) among persons undergoing HIV antibody testing while Gala *et al.* (1989) found both higher rates of psychopathology and increased numbers of attempted suicides in HIV negative 'at risk' homosexual men and intravenous drug-users when compared to heterosexual controls.

From the above it appears that anxiety, depression, and personality disturbance occur commonly in persons at risk for HIV infection. Thus, discussion of psychological effects of HIV infection needs to account for this elevated base rate.

SEROCONVERSION PHENOMENA

Most persons do not know when they became infected with HIV. Indeed, substantial numbers of at risk persons, particularly in the intravenous drug-using group, continue to deny that they could become infected, or alternatively, take the fatalistic viewpoint that they probably are already infected, and therefore should not worry. Still others acknowledge their risk on an intellectual plane but feel powerless to alter their behaviour when swept up in the maelstrom of drug-using or sexual activity that places them at risk.

On the other side of the continuum are the 'worried well' (Miller *et al.* 1988). These are seronegative individuals (who have often tested repeatedly seronegative) who nevertheless remain convinced that they harbour the infection. The 'worried well' can exhibit a variety of hypochondriacal complaints, including fatigue, vague aches and pains, difficulties with memory and concentration, gastrointestinal and genitourinary symptoms, respiratory complaints, headaches, and other nonspecific symptoms. Counselling and general support are sometimes helpful, especially in a group-therapy setting. In some instances the symptoms and accompanying worry become a constant preoccupation or wax and wane in intensity depending on other circumstances in the person's life.

For persons who actually become infected with HIV, antibody tests will become positive several weeks to several months after exposure (not everyone who is exposed becomes infected, however); also, in rare instances, the delay from infection to seroconversion may be prolonged for a year or more (Imagawa *et al.* 1989).

At the time seroconversion occurs, some patients experience seroconversion illness, very similar in character to a flu-like syndrome. There may be fatigue, malaise, low-grade fever, aches and pains, and, on occasion, signs of meningeal irritation – headache, photophobia, stiff neck. It is not known whether those who experience meningeal symptoms during seroconversion are more likely to have neurogenic consequences later. From a medical standpoint, the seroconversion illness is transient and the individual returns to his or her ordinary state of health within days or weeks to enter the asymptomatic phase of HIV infection.

DISCOVERY OF SEROSTATUS

As might be expected the period surrounding antibody testing and notification of results can be stressful. Interestingly, research involving structured questionnaires reveals only modest upswings in anxiety and depression ratings (Jadresik *et al.* 1989). Studies on coping responses indicate a sense of alienation can accompany recent knowledge of serostatus (Korniewicz *et al.* 1989). Mood measures tend to normalize in seropositives from nine weeks to six months after notification (Fishman *et al.* 1989; Jadresik *et al.* 1989). Persistence of distress in the longer term appears to be inversely related to perceived social support and ‘hardiness’ (Fishman *et al.* 1989).

ASYMPTOMATIC AND EARLY SYMPTOMATIC PHASES OF INFECTION

After seroconversion persons who become HIV antibody positive typically remain free of medical symptoms for a prolonged period of time. While the progress of the underlying infection can be documented by slow decline in CD4 cell numbers, until an individual’s count falls to 400 or below medical complications are uncommon. Indeed, many persons remain medically asymptomatic until their CD4 numbers drop to 200 or lower (normal persons generally have numbers above 1000 per cubic ml).

There has been considerable attention focused on psychological and neurocognitive characteristics of this asymptomatic period, which typically lasts five to eight years (some remain asymptomatic longer; it is not known whether a person can remain asymptomatic permanently).

While most observers would agree that medically asymptomatic seropositive individuals experience some increase in psychological distress compared to seronegative controls, the qualitative and quantitative features of such distress have depended on specific samples studied and methodologies employed. For example, symptoms of anxiety, determined by self-report checklists (whether self-rated such as the State Trait Anxiety Inventory; or observer-rated, such as the Hamilton) tend to be higher in medically asymptomatic HIV positive persons than HIV negative ‘at risk’ samples (Atkinson *et al.* 1989; Coumartin *et al.* 1989; Hems *et al.* 1989). Self report of depressive symptoms also tends to be higher in seropositives than seronegatives, though not as elevated as that reported by patients with AIDS Related Complex (ARC) and AIDS (Atkinson *et al.* 1988; Coumartin *et al.* 1989; Hems *et al.* 1989). Individuals with perceived lack of social support tend to be particularly depressed (Ostrow *et al.* 1989).

If structured psychiatric interviewing and rigorous diagnostic criteria (e.g. Diagnostic Interview Schedule (DIS)) are used to assess mood disorders, then the proportion of persons during this stage who experience anxiety (using a six month incidence for the rate) is approximately 20% (Atkinson *et al.* 1988). While this rate is somewhat higher than for seronegative ‘at risk’ controls (10%) it is not statistically significantly so; and the latter rate greatly exceeds the negligible six month incidence of diagnosed anxiety among HIV negative heterosexual controls. The incidence of depressive episodes is similar: HIV positive asymptomatic persons are more likely to have an episode of depression (e.g. 6 month incidence of 8 to 19% in the two studies reported by Atkinson *et al.* 1988, 1989, and 13.4% by Coumartin *et al.* 1989). Interestingly, these rates are comparable to the 13.9% six month prevalence of mood disorders recorded for at risk persons undergoing HIV testing (i.e. persons who did not yet know their serostatus – Jacobsberg *et al.* 1989).

In sum, data on mood disturbance during the medically asymptomatic period indicate that

10–20% of these individuals will experience an episode of anxiety, depression, or both during a preceding six month period. While the rates for seronegatives who are in various 'risk' groups tend to be lower, they still exceed those for matched persons who are 'not at risk'. This indicates that psychiatric phenomenology in the context of asymptomatic HIV infection must be understood as an interaction between predisposition to mood disturbances and response to knowledge of serostatus.

With regard to 'neurogenic' phenomenology, considerable attention has been devoted to determine whether neurocognitive changes can be detected early in the course of the HIV infection. The press to do so has been stimulated by the common observation that perhaps a third of persons with advanced AIDS become clinically demented and another third may manifest subsyndromal pathology in the form of varying degrees of neuropsychological deficit (Grant & Heaton, 1990).

Early observations by our group indicated that a substantial proportion of medically asymptomatic seropositive persons might have mild neuropsychological deficit (in that study, seven of sixteen such persons had neuropsychological abnormality *versus* one of eleven HIV negative homosexual controls, Grant *et al.* 1987). We have also reported increased neuropsychological and brain magnetic resonance imaging (MRI) abnormalities in a recently completed study at St Mary's Hospital and Queen Square (Grant *et al.* 1990).

While there is general agreement that persons with ARC and AIDS are at heightened risk for neuropsychological and other neurobehavioural abnormalities, the status of persons in the earlier phases of the disease remains controversial (Grant & Heaton, 1990; Marotta & Perry, 1989). A review of the most recent presentations on this topic, which occurred at the Fifth International AIDS Conference in Montreal, Canada in June of 1989, shows the number of studies demonstrating some early neurobehavioural abnormality to be about equal to those concluding that HIV positive medically asymptomatic persons are entirely normal from a neurobehavioural standpoint. Among studies reporting positive results, HIV + medically asymptomatic persons have been found to show subtle impairments on neuropsychological tests (Van Dis *et al.* 1989; Stern *et al.* 1989; Chave *et al.* 1989; Clifford *et al.* 1989; Collier *et al.* 1989; Martin, A. *et al.* 1989); abnormalities on reaction time measures (Miller, E. N. *et al.* 1989*b*; Martin, E. *et al.* 1989); various electrophysiological abnormalities (Koralnik *et al.* 1989; McAllister *et al.* 1989; Ollo *et al.* 1989), eye movement abnormalities (Currie *et al.* 1989) and abnormality on magnetic resonance imaging (MRI) (Coats *et al.* 1989; Collier *et al.* 1989). In addition, a recently published report indicated subtle neuropsychological impairment in seropositive asymptomatic, immunocompetent men when compared to seronegative controls (Perry *et al.* 1989).

In contrast to research reporting subtle abnormalities in HIV positive asymptomatic persons is an array of studies failing to document such changes. They include neuropsychological investigations (Goethe *et al.* 1989; Visscher *et al.* 1989; Selnes *et al.* 1989; Saykin *et al.* 1989; Miller, E. N. *et al.* 1989*a*, 1990); as well as reaction time studies (Perdices & Cooper, 1989) and studies on vibrotactile thresholds (Franzblau, 1989). Data from the US Multicenter AIDS Cohort study also failed to document any MRI differences between HIV positive and negative persons (McArthur *et al.* 1988, 1989*b*).

Despite these disagreements, we think it premature to dismiss the positive studies on the basis of sampling problems, methodological defects, and the like. Perhaps the strongest reason for keeping an open mind comes from observations that cerebrospinal fluid (CSF) abnormalities are common in asymptomatic persons. For example, as many as 50% of HIV positive persons have abnormal numbers of white cells in the CSF and about a quarter have abnormal amounts of protein. Intrablood brain barrier IgG synthesis was reported elevated in 88% of asymptomatic persons in one study (Singer *et al.* 1989). Furthermore, these CSF abnormalities appear to be progressive (Marshall *et al.* 1989*a, b*; McArthur *et al.* 1989*a*). Most worrisome is the fact that HIV can be cultured from the CSF of approximately half of asymptomatic individuals (McArthur *et al.* 1988). While the presence of virus in the CSF does not prove it is in the brain, such observations, when coupled with frequent (though contradictory) reports of early subtle neurobehavioural ab-

normalities must continue to be taken seriously. Several large scale prospective studies are now under way, some of which are examining recent seroconverters for whom dates of change in serostatus are reasonably well established. Through such longitudinal multidisciplinary studies it should be possible to arrive at a clearer understanding of the actual risk for neurogenic disturbance in the asymptomatic individual.

FINDINGS IN PATIENTS WITH AIDS AND AIDS RELATED COMPLEX

With the decline in cellular immunity reaching a point at which opportunistic infections and other diseases become more prominent the patient enters the symptomatic phases of illness, ARC and AIDS. While 'psychogenic' disturbances can continue to be prominent (for example, 20–30% of patients with AIDS reach criteria for anxiety or depressive disorder, see Perry & Tross, 1984; Holland & Tross, 1985), behavioural abnormalities which are secondary to brain disease acquire increasing salience.

Comprehensive neuropsychological testing reveals deficiencies in learning, problem solving, and speeded information processing in roughly half of patients defined as having ARC and up to three-quarters of those having frank AIDS (see review by Grant & Heaton, 1990). It is estimated that approximately one-third of patients with AIDS will develop frank dementia. One prospective study found the two year incidence of clinical dementia in a two year follow-up of ARC/AIDS patients to be 28% (Day *et al.* 1989).

The most common causes of central nervous system (CNS) disease are thought to be HIV encephalitis, toxoplasmosis, and co-infection with cytomegalovirus. Many other viruses and pathogens can infect the CNS later in the course of AIDS, and primary lymphomas can also complicate the picture (for review, see Dalakas *et al.* 1989).

Beside neuropsychological testing, magnetic resonance imaging appears to be particularly sensitive in identifying brain disease early in the course of AIDS. In previous work we noted that 75% of MRI scans from AIDS patients were abnormal as were 50% of those with ARC (Grant *et al.* 1987, 1988). Common patterns of abnormality included multiple focal lesions, larger confluent areas of white matter involvement and basal ganglion involvement, brain atrophy (dilated ventricles, enlarged sulci), and the occasional solitary lesion. Studies with Positron Emission Tomography (PET) suggest that there may be hypermetabolism in subcortical structures earlier in the evolution of the AIDS dementia complex but hypometabolism later (Price *et al.* 1988).

The manner in which HIV affects the brain is poorly understood. It is evident that neurons themselves are rarely infected, but surrounding cells and mononuclear elements in particular are. On microscopic examination, HIV associated pathology includes 'myelin pallor', and foci of multinucleated giant cells from which HIV can be recovered. Endothelial cells of brain vessels can also be infected, and this may contribute to the pathological process. Wiley *et al.* (1986) have theorized that infected mononuclear cells may release substances which are toxic to neurons (e.g. tumor necrosis factor and other lymphokines). It may be that fragments of the virus which have homology with neurotrophic factors such as vasoactive intestinal peptide (VIP) may interfere with peptide regulation of neurons. The observation that the gp120 structural protein of HIV has some similarity to VIP has led to tests with synthetic peptides (e.g. peptide T) which might block the effects of gp120. At the moment, it is not clear whether therapeutic trials with peptide T will be successful in protecting against CNS disease.

Another intriguing observation has been that quinolinic acid, a neurotoxic metabolite of tryptophan, can be found at higher concentrations in the CSF of HIV-infected persons, particularly those exhibiting neurological signs. This leads to the possibility that HIV may disrupt tryptophan metabolism, shunting the degradation of this biogenic amine through an abnormal biochemical pathway (Heyes *et al.* 1989).

Another recent observation has suggested that CSF 5-hydroxyindoleacetic acid (a metabolite of serotonin) is decreased in HIV-infected persons. If this is replicated, it is conceivable that some of

the behavioural disturbances in ARC and AIDS (in particular, depression and apathy) may be related to reductions in brain serotonin activity.

RELATIONSHIP OF ANTI-HIV TREATMENT TO BEHAVIOURAL ABNORMALITY

The anti-retroviral agent zidovudine (azidothymidine, AZT) can decrease, at least for a time, medical complications and prolong life in HIV-infected persons. To what extent drugs such as zidovudine can also protect against or reverse neurological complications remains unclear. There have been reports of neuropsychological improvement in AZT treated persons compared to controls (Schmitt *et al.* 1988; Price *et al.* 1989; Sidtis *et al.* 1989). On the other hand, our study on incidence of dementia showed that 28% of AIDS and ARC patients developed clinical dementia despite most of them having received zidovudine (Day *et al.* 1989). Thus, while current anti-retroviral agents might slow, or even temporarily benefit, neuropsychiatric sequelae, the long range prognosis may not be so favourable.

SUMMARY: CHALLENGES FOR THE FUTURE

HIV infection can produce a neurobehavioural disorder as well as an immunological disease. Persons at various stages of HIV infection are more likely to have symptomatic anxiety, depression, adjustment disorders, and other behavioural disturbances. While some of these 'psychogenic' changes clearly can be related to knowledge of HIV infection and its probable consequences, they should not all be ascribed to the stress of illness. Rather, in Western societies at least, those who are at risk for HIV infection also appear to have higher background rates of psychological disturbances. Thus, the evaluation and management of psychiatric disturbances needs to take into account these two likely factors in the aetiology of current problems.

HIV infection also brings with it the burden of direct injury of the central nervous system with consequent impact on neurocognitive functioning. Medically asymptomatic or mildly symptomatic persons may have a small but significant risk for neurobehavioural disturbance compared to seronegatives; however, the data here remain conflicting. By the time an individual reaches ARC or AIDS, the likelihood of such disturbance increases substantially. Neurobehavioural abnormalities can range from subtle disturbances in cognitive function (memory and speeded information processing in particular) to frank dementia which has often been described as having 'subcortical' features – i.e. a greater weight of symptoms in the areas of slowed information processing, defective learning, but with sparing of language ability until later stages).

There are many important directions for future research, but several are of particular relevance to those involved in psychological medicine. A pressing need is to define the incidence, qualitative features, and natural history of CNS involvement of HIV infection; to determine whether there are 'neurotropic' strains of HIV; to document the importance of co-infection with other viruses; and to elucidate host factors (genetic, constitutional, previous medical history) which may facilitate CNS disease. Additional research needs to address the role of stress in speeding progress of disease, and its neurobehavioural consequences.

In summary, the tragedy of HIV presents both opportunities and challenges to investigators and practitioners of psychological medicine to contribute to improved characterization, treatment, and prevention of AIDS and its neurobehavioural consequences.

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