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Neuropsychological Dysfunction among HIV Infected Drug Abusers

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Abstract: Human immunodeficiency virus (HIV) has been documented to cause direct and indirect central nervous system dysfunction that can be observed as a progressive decline in neuropsychological functioning in a large proportion of persons with HIV and AIDS. Neuropsychological decline in individuals with HIV is characterized by cognitive and motor slowing, attentional deficits, executive dysfunction and memory impairment (characterized by intact recognition and deficits in learning and delayed recall). Dementia occurs in a relatively small proportion of HIV infected individuals, though milder NP deficits are observed in 30-50% of persons with advanced disease. Recent evidence suggests that drug users, especially stimulant users, are at risk for accelerated progression of their HIV disease, including a greater risk of neuropsychological dysfunction. Methamphetamine may potentiate HIV Tat protein mediated neurotoxicity giving rise to striatal proinflammatory cytokine stimulation and activation of redox-regulated transcription factors. Oxidative stress due to mitochondrial dysfunction is another candidate process underlying the synergistic effects of stimulant use and HIV. Damage to neurotransmitter systems including the dopaminergic, serotonergic and glutamatergic systems which are affected by both stimulant use and HIV is an alternate explanation. Methamphetamine has also been shown to impede the effectiveness of HAART, which could then in turn allow for more rapid HIV disease progression. A greater prevalence of psychiatric disorders, particularly mood, anxiety and substance use disorders are also observed in HIV positive samples relative to the general population. The changing nature of the HIV pandemic is an ongoing challenge to investigators and clinicians working in this field. Emerging issues requiring additional attention are study of the interactive effects of normal aging and HIV on neurocognition as well as study of the effects of co-infection with Hepatitis C.

Key words: HIV, AIDS, Neuropsychology, Drug Abuse

INTRODUCTION

The neuropsychological effects of human immunodeficiency virus (HIV): Human immunodeficiency virus (HIV) has been documented to cause direct and indirect central nervous system dysfunction[1-3] which can be observed as a progressive decline in neuropsychological functioning in a large proportion of persons with HIV and AIDS. Neuropsychological dysfunction due to HIV infection can occur through two basic mechanisms. First, immunocompromised patients are at increased risk for developing opportunistic infections of the brain such as toxoplasmosis and progressive multifocal leukoencephalopathy. Alternatively, HIV can directly cause neuropsychological dysfunction. The neuropsychological deficits that accompany HIV can range from mild cognitive symptoms to full-blown dementia. Neuropsychological decline in individuals with HIV is characterized by cognitive and motor slowing, attentional deficits, executive dysfunction and memory impairment (characterized by intact recognition and deficits in learning and delayed recall)[4-7]. Several studies have employed measures from cognitive and experimental studies in an attempt to deconstruct the attentional and processing speed deficits observed in HIV[8-9]. This work has suggested that tasks which place a high demand on controlled attentional processing as compared to automatic processing are more compromised in HIV infected persons[10]. Language, visuospatial and global cognitive functioning are typically intact in the earlier stages of illness with substantial deficits observed only in late stage illness or in demented individuals. Symptoms of cortical dementias such as apraxia, agnosia and aphasia are absent unless patients develop a CNS opportunistic infection or neoplasm.

Dementia occurs in a relatively small proportion of HIV infected individuals, though milder NP deficits are observed in 30-50% of persons who are symptomatic or have AIDS[3, 6]. The advent of HAART has resulted in a markedly lower incidence of HIV related neurobehavioral disorders[11-12], though prevalence rates are now climbing as patients are living longer. However, such gains will not be observed among patients who fail to adequately adhere to their

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medication regimen. Poor medication adherence has been linked to neurocognitive deficits, particularly executive dysfunction and memory deficits, with such associations exacerbated among older adults[13-14].

In general, the severity of NP deficits increases with disease progression as well as severity of immunocompromise. Studies examining more severely immunocompromised individuals, particularly those with AIDS, have found greater neuropsychological impairment in those with advanced disease compared to seronegative controls. The presence of AIDS defining illness is associated with greater NP performance on domains such as executive functioning, psychomotor speed and global NP performance[15]. Neurobehavioral declines are generally not observed in infected persons in the early stages of the disease[16-18], unless other co-factors such as low education, substance use and other premorbid CNS risk factors are also present[19]. Many NP studies of HIV were conducted prior to the advent of HAART and it has been suggested that in the HAART era, duration of disease may be the primary risk factor for neurocognitive compromise independent of CD4 count[20].

American Academy of Neurology (AAN) criteria for HIV related neurobehavioral disorders distinguish the subtypes on the basis of severity. Both HIV-associated dementia and HIV-associated minor cognitive-motor disorder are characterized by memory difficulties, motor and psychomotor slowing, slowed information processing, attentional disruption and executive dysfunction. With the advent of HAART, some have suggested that the natural history of HIV dementia has been altered. McArthur *et al*.[21] have offered an alternative formulation and have posited three dementia subtypes: chronic active, chronic inactive and subacute progressive, the latter bearing similarity to the clinical manifestations of HIV dementia prior to the development of HAART.

Structural neuroimaging such as MRI is typically unremarkable until later stages of disease progression at which time cortical atrophy and ventricular enlargement can be visualized[22-23]. Studies using PET with fluorodeoxyglucose have revealed a two-stage process, with basal ganglia hypermetabolism present initially followed by global hypometabolism in later stages[24-25]. PET using [11^{C}] cocaine has found decreased levels of dopamine transmitters (DAT) in the striatum of demented, but not non-demented, HIV-infected patients[26]. Reductions in striatal DAT have also been reported to occur in methamphetamine abuse[27]. Proton MR spectroscopy (^{1}H MRS) is notable for elevated choline/creatine (a marker of neuronal damage)and decreased *N*-acetyl aspartate/choline ratios (indicative of gliosis) in frontostriatal regions[28]. Similar findings have also been reported in methamphetamine abusers[29].

The independent and interactive effects of HIV and substance use and neuropsychological functioning: There exists a substantial, though often contradictory, body of work describing the neuropsychological effects of substance use and abuse on neuropsychological performance among HIV infected individuals. Research examining the neurocognitive effects of drug abuse among HIV infected adults is fraught with methodological pitfalls. Precise measurement of drug use is often problematic given poor recall, variable patterns of drug use and occasional lack of candor in self-reported drug use. Poly-drug use is also common, a confound that can complicate attribution of adverse drug effects to any single substance. Co-factors which frequently accompany drug use include lower socioeconomic status, nutritional abnormalities, lower education levels, histories of head injury or other neurological compromise and higher rates of psychiatric disorder, all of which can complicate interpretation of the effects of drug use.

Methodological limitations aside, the relatively high rates of drug use, particularly stimulant use[30-31] and alcohol use[32-33] among HIV infected adults highlight the need to examine not only the independent effects of HIV on neuropsychiatric and neurocognitive function but the independent and potentially interactive effects of concurrent drug use. Furthermore, recent evidence converges on the conclusion that drug users are at risk for accelerated progression of their HIV disease[34]. Numerous studies have attempted to examine the synergistic effects of drugs of abuse and HIV on disease progression and neuropsychological functioning, with surprisingly mixed results. A number of studies have failed to demonstrate evidence of an additive/interactive effect of HIV and substance use, instead describing independent effects of HIV and drug use[35-39]. Some studies have reported no differences between asymptomatic injection drug users and seronegative controls[35, 40]. Bornstein *et al*.[38] noted that neither recency nor severity of drug or alcohol abuse and dependence were associated with NP impairment in HIV infection – however, the drugs of abuse were not clearly specified in their study. Basso & Bornstein[15] obtained no independent or interactive (with HIV) effect of past drug abuse on NP function and posit that past drug use may not influence current NP function, or that only more sensitive measures (e.g. reaction time) of neurocognition would be vulnerable to independent and possibly interactive effects of drug use and HIV, suggestions which are supported by other studies[39].

In contrast, others have demonstrated an additive effect between HIV and substance use, particularly methamphetamine use. In the last 5 years, methamphetamine has become one of the most frequently abused drugs in HIV infected samples[41]. Levine *et al*.,[42] compared HIV+ persons both with and without recent stimulant (either cocaine or

methamphetamine) use. Those who had used stimulants recently revealed increasing rates of attentional disruption compared to a drug-free HIV+ comparison group. Similarly, Rippeth *et al*.[43] observed a trend across groups which varied as a function of HIV status and methamphetamine dependence with the greatest NP impairment observed in those with both methamphetamine dependence and HIV. Deficits were observed on global NP function and specifically on measures of attention/working memory, learning, recall and motor functioning. Among HIV+ persons abusing methamphetamines, persons with greater immunosuppression[44] have been found to have the highest rates of NP impairment, lending support to an additive relationship between HIV, immune function and drug use on NP function. Martin *et al*.[45] has also documented poorer auditory working memory in HIV+ vs. HIV- polydrug users. Durvasula *et al*.[39] examined a large cohort of African American men (n=237) from the African American Health Project (AAHP) who were recruited on the basis of cocaine use history and HIV seropositivity. In this cohort, moderate to heavy recent cocaine use, confirmed using urine toxicology assays, was associated with slower psychomotor speed but did not appear to adversely affect other neurocognitive domains.

Several neurophysiologic mechanisms have been advanced as candidate explanations for why stimulant use may exacerbate the deleterious neurological effects of HIV. Methamphetamine has been shown to potentiate HIV Tat protein mediated neurotoxicity in animal models, giving rise to striatal proinflammatory cytokine stimulation and activation of redox-regulated transcription factors[46]. Oxidative stress due to mitochondrial dysfunction is another candidate process underlying the synergistic effects of stimulant use and HIV. Damage to neurotransmitter systems including the dopaminergic, serotonergic and glutamatergic systems which are affected by both stimulant use and HIV is an alternate explanation[47,48]. Multiple studies have shown HIV disease progression to be accelerated among drug abusers[34]. Methamphetamine has also been shown to impede the effectiveness of HAART, which could then in turn allow for more rapid HIV disease progression[49].

In general and particularly in HIV infected cohorts, alcohol and drug use are commonly confounded, making it difficult to definitively draw conclusions about the contribution of either in isolation. Green *et al*.[50] examined a sample of HIV- and HIV+ men with a history of modest alcohol consumption during the past year, varying histories of alcohol abuse and matched on drug use histories. They found that alcohol and HIV exerted independent effects on cognitive performance but failed to find an interaction effect. In contrast, Durvasula *et al*.[51], using data from the above referenced AAHP study, did demonstrate an interaction between HIV and alcohol use, with HIV+ heavy drinkers evidencing disproportionately poorer performance on measures of reaction time and motor speed relative to HIV+ subjects who did not drink to excess.

Neuropsychiatric features of HIV and substance use: A greater prevalence of psychiatric disorders, particularly mood, anxiety and substance use disorders are observed in HIV positive samples relative to the general population[52]. Apathy, irritability and higher rates of depressive symptomatology are also frequently observed[52-53]. Unlike neurocognitive deficits, which tend to increase with disease progression, rates of psychiatric disorders do not vary as directly as a function of disease stage. Symptoms which are more likely a by-product of direct CNS involvement, such as apathy and irritability are however, more common in advanced disease[54].

Etiologically, the psychiatric sequelae of HIV represent both direct effects of the virus on frontostriatal function as well as indirect results of the psychosocial burdens engendered by the illness. Castellon *et al*.[53-54] have linked apathy, irritability and aspects of depression to neurocognitive dysfunction in HIV and suggested a common etiological basis. Psychosocial burdens such as medical stressors, economic issues, stigmatization and marginalization associated with HIV/AIDS may also independently drive the development of psychiatric symptoms.

Far less work has focused on the co-occurrence of personality disorders (PD) among HIV-infected substance users. Rates of PD in substance abusing samples are significantly higher than in normal cohorts[55], with antisocial personality disorder evidencing the highest rates of comorbidity with substance abuse[56]. Some sources have even described APD as being a better predictor of cognitive dysfunction than drug use severity[57]. Widely varying prevalence estimates of personality disorder in HIV infected samples have been noted with estimates ranging from 18 – 61%[58-59]. This is in contrast to lower rates of personality disorders in seronegative samples of 15-20% and in community samples of 1 to 11%[60-63]. Disorders characterized by impulsivity and interpersonal and affective instability (Cluster B) are most prevalent in HIV + samples, with borderline (BPD) and antisocial (ASPD) personality disorder most common in HIV+ PD patients[59,64-67].

Both personality disorders and specific traits, such as sensation seeking should be considered in any comprehensive description of the neuropsychiatric picture of HIV and substance use.

New challenges: The changing nature of the HIV pandemic is an ongoing challenge to investigators and clinicians working in this field. The impact of comorbid Hepatitis C infection among HIV-infected drug abusers

has received increasing, albeit to date insufficient, attention. Several studies have found HIV/HCV co-infection to be associated with an increase risk of neuropsychological compromise[68-72]. Neurometabolic commonalities between HIV and HCV such as elevated creatine levels in frontostriatal regions provide the basis for hypothesizing that the co-occurrence of these two viruses among drug abusers may be particularly problematic.

With the decrease in mortality secondary to improvements in antiretroviral therapies, the HIV-infected population has continued to age. As a result, the untoward effects of the normal aging process on cognition and on immunological function, not to mention pathological processes such as Alzheimer's disease and cerebrovascular disease, will increasingly complicate the neurobehavioral expression of HIV infection. Higher rates of neuropsychological deficits have been found among older HIV+ adults[73-75], with age over 50 years increasing the likelihood of cognitive impairment by 50%[76].

Although women comprise an increasingly large percentage of HIV-infected drug abusers, considerably less work on the NP sequelae of HIV and drug use has been conducted with women. While some studies employed gender-mixed cohorts, women typically comprise a small fraction of the sample and as such, the findings still predominantly reflect the performance of men to the relative underepresntation of women. Investigations that have focused solely on samples of women have found that women evidence deficits in psychomotor speed, attention and memory[77-78], with recent exposure to drugs also associated with NP performance. In general, while women evidence similar patterns of NP performance as a function of HIV, less work has been conducted to examine the onset of such deficits as a function of disease progression. Women are also more likely to present with more advanced disease at the time of HIV diagnosis. Consideration of other gender specific factors such as the impact of estrogen on NP performance in HIV+ women is necessary, given the putative neuroprotective effects of both exogenous and endogenous estrogen[79] and the rapidly increasing rates of new infection in women. Linkage of genetic polymorphisms with their phenotypic manifestations, including focus on gene X environment interactions, is yet another challenge to be faced by HIV researchers.

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