Effect of Chronic Alcohol Abuse on the CNS Morbidity of HIV Disease

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CNS DISEASE is a frequent cause of human immunodeficiency virus (HIV) morbidity and mortality. The newest “successful” treatments for HIV disease, the protease inhibitors, have limited CNS penetration. Because of this, CNS morbidity may become even more important in the management of HIV disease. There is a high prevalence of heavy alcohol use in populations at high risk for HIV infection; however, there is little research addressing the effect of heavy alcohol use on the severity and course of HIV disease. Moreover, the toxicity of heavy alcohol use alone can result in CNS morbidity in otherwise healthy individuals. Although in many cases the insults of chronic heavy alcohol use and HIV disease may independently not be sufficient to yield clinically significant findings, their cumulative effects may result in clinical signs of impaired CNS functioning.

We used event-related brain electrical potentials (ERPs) as indices of information processing operations to study the brain effects of alcohol abuse alone, HIV disease alone, and the comorbidity of alcohol abuse and HIV disease. We focused on the latency of the P3A ERP component, which reflects a frontal cortex-mediated orienting response to rare and/or novel events. We sought to: (1) determine whether P3A latency is delayed as a result of the morbid effects of chronic alcohol abuse, (2) establish the sensitivity of P3A latency to HIV CNS morbidity, and (3) examine P3A latency in the face of both chronic alcohol abuse and HIV disease.

P3A LATENCY IS DELAYED IN ELDERLY MALE CHRONIC ALCOHOLICS WITH LONG-TERM ABSTINENCE

We investigated the effects of alcohol abuse on P3A latency in older male chronic alcoholics with long-term (9.0 ± 6.6 months) abstinence. We studied older male alcoholics because the CNS morbidity of chronic alcohol abuse is thought to be largest and most persistent in both older people and in males. Twelve older abstinent chronic alcohol abusers (age: 61.7 ± 8.5 years) and 11 older controls (age: 62.5 ± 10.2 years) were studied in auditory and visual three-condition P3A paradigms with standards, targets, and novel rare nontargets. In this paradigm, the P3A component is reliably elicited in response to the novel rare nontarget stimuli. P3A latency was delayed in both modalities in the abstinent older chronic alcoholics, compared with the controls (Fig. 1; auditory: 362.7 vs. 334.9 msec, p = 0.038; visual: 401.3 vs. 364.7 msec, p = 0.003). P3B in the target condition tended to also be delayed in the older chronic alcoholics in the auditory modality (398.3 vs. 377.8 msec, p = 0.065) and was delayed in the visual modality (474.3 vs. 412.0 msec, p = 0.004). There were no P3A or P3B amplitude effects, nor were there any latency or amplitude effects on earlier components, indicating that the P3 latency effects were not the result of delays in sensory processing or in processes associated with earlier ERP components. Analysis of covariance (ANCOVA) showed that the P3A and P3B latency effects were independent of each other. These results indicate that: (1) both P3A and P3B latency delays are evident in older abstinent chronic alcoholics, (2) separate mechanisms may be responsible for these effects, and (3) these effects are more sensitively detected in the visual versus the auditory modality. These ERP abnormalities occur in the context of persistent neuropsychological deficits (primarily in memory and visual/spatial functioning). We have additional data from magnetic resonance spectroscopic imaging that shows a reduction of N-acetyl aspartate (NAA) in the frontal cortex of these older alcoholics. NAA is a compound thought to be unique to neurons; therefore, a reduction in NAA (especially in the absence of atrophy on structural magnetic resonance imaging, as is the case in this sample) is suggestive of neuronal loss and/or damage.

P3A LATENCY IS DELAYED IN HIV DISEASE: THE MAGNITUDE OF THIS DELAY COVARIATES WITH THE SEVERITY OF COGNITIVE IMPAIRMENT

We investigated the effects of HIV disease on the delay of the frontal cortex-mediated P3A orienting response in the absence of alcohol abuse. We studied 16 severely cognitively impaired HIV+ subjects, 20 mild to moderately cognitively impaired HIV+ subjects, and 35 cognitively normal

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HIV+ subjects, and 17 HIV− gay/bisexual (i.e., high-risk) controls. All subjects were studied in the auditory modality; visual modality studies were begun about one-third of the way through the study. Auditory P3A latency was delayed by 12 msec in the cognitively normal HIV+ group, compared with HIV-controls ($p < 0.024$; Fig. 2). The HIV disease-associated delay in both auditory and visual P3A latency increased with increasing severity of HIV-associated cognitive impairments ($p = 0.0001$). The latencies of earlier ERP components were also examined. The only significant finding was an increase in P200 latency; however, the P3A latency effect remained (at $p = 0.003$) after removing the effect of the P200 latency delay via ANCOVA. The P3A latency delay therefore indicates an abnormality that occurs after sensory processing of stimuli. Finally, auditory and visual P3A latencies were highly correlated, despite topographic evidence for different generators. This leads us to speculate that the delayed P3A latency may reflect deficits in striatal or thalamic outputs to the P3A generation system or delays in transmission from striatal or thalamic sites to the P3A generators.

**P3A LATENCY REFLECTS THE COMORBIDITY OF ALCOHOL ABUSE AND HIV INFECTION**

We examined the P3A latency effects of chronic heavy alcohol use and HIV infection in light/nondrinking and chronic heavy drinking HIV+ samples that were matched on percent CD4 lymphocytes. The matching of samples on severity of systemic immunosuppression in this design renders the study blind to any synergistic effects of HIV disease and chronic heavy alcohol use that are manifest as systemic immune suppression (study design issues are discussed in more detail herein). However, the design allows determination of the sensitivity of P3A latency to the effects of HIV disease and current chronic heavy alcohol use, and is sensitive to any HIV/alcohol synergy that takes place solely within the CNS.

We studied samples of HIV+ chronic heavy drinkers ($n = 31$), HIV+ light/nondrinkers ($n = 37$), HIV− chronic heavy drinkers ($n = 18$) and HIV− light/nondrinkers ($n = 16$). The age range of the HIV− subjects was 22 to 57 years (mean: $37.0 \pm 9.7$ years) for the light/nondrinkers and 24 to 55 years (mean: $40.5 \pm 10.0$ years) for the chronic heavy drinkers, with comparable age ranges and means for the HIV+ subjects. The HIV+ samples were matched on percent CD4 lymphocytes, and the heavy drinker samples were matched on alcohol consumption. P3A latency exhibited additive effects of chronic alcohol abuse (a $17$ msec increase; Fig. 3 white bars; $p = 0.005$) and HIV seropositivity (a $10$ msec increase; $p = 0.05$). In HIV+ light/nondrinkers, P3A latency delays occurred primarily in subjects whose clinical disease had advanced to CDC clinical stages B and C, whereas in HIV+ chronic heavy drinkers, P3A latency delays...
delays occurred even in asymptomatic seropositive subjects. There were no effects of either alcohol use or HIV status on P3B latency. P3B amplitude was unaffected by HIV status, but was reduced in chronic heavy drinkers (likely reflecting genetic risk factors for alcohol abuse). There were no latency or amplitude effects on earlier sensory components. The auditory modality latency remained. We have recently strongly replicated these results in new samples using ANCOVA, the additive effects of alcohol use and HIV on P3A latency remained. We have recently strongly replicated these results in new samples using high-risk HIV-controls. Data from the replication study are represented by the hatched bars in Fig. 3.

DISCUSSION

The aforementioned three studies demonstrate that P3A latency is sensitive to: (1) the effects of chronic heavy active alcohol use in HIV—individuals; (2) the effects of HIV disease in cognitively normal HIV+ subjects, with greater effects in HIV+ subjects with mild to severe cognitive impairments; (3) the persistent effects of chronic alcohol abuse in older chronic alcoholics with long-term abstinence; and (4) the additive effects of chronic heavy active alcohol use and relatively early-stage HIV disease. Our future research goes a step beyond these additive effects of alcohol abuse and HIV disease to propose a model that addresses possible synergistic effects of alcohol abuse and HIV disease on the CNS.

A model of the potential synergistic effects of chronic heavy alcohol use and HIV disease is presented in Fig. 4. In this model, there are no effects of alcohol use or HIV disease in HIV—light/nondrinkers. The direct toxic CNS effects of alcohol use (the double-lined box) can be measured in HIV—heavy drinking subjects. Systemic HIV disease has associated CNS morbidity (the single-lined box), as depicted in HIV+ light/nondrinking subjects. The final column illustrates the CNS morbidity predicted by the synergistic model (the bold box) in HIV+ heavy drinking subjects.

The HIV+ heavy drinking subjects can suffer CNS morbidity from three sources: (1) the direct toxic effects of alcohol, (2) the CNS sequelae of HIV systemic disease (comparable in magnitude to that of HIV+ light/nondrinking subjects), and (3) the CNS sequelae of any increased HIV systemic disease brought about by chronic heavy alcohol use (the synergistic effect). We hypothesize that HIV and heavy alcohol use have a synergistic effect on the CNS as a result of: (1) behavioral effects of heavy alcohol use on treatment seeking, treatment adherence, nutrition, or risk behaviors (which could lead to repeated inoculations with new viral strains); and (b) biological effects of heavy alcohol use on nutrition and the metabolism and drug levels of treatment medications.

The Multicenter AIDS Cohort Study (MACS),6 a classic cohort design, showed little or no effect of heavy drinking on the progression of HIV disease. However, the “heavy drinkers” of that study included very few truly abusive drinkers. The median alcohol consumption of the heavy drinkers in that study was 15.7 drinks/week, only 3 to 4 drinks/week over the 2 drinks/day considered nonabusive consumption and only two-thirds of the minimum alcohol consumption of our heavy drinking HIV+ samples in the studies described herein. There may be threshold of alcohol use above which the behavioral and biological phenomena associated with chronic heavy alcohol use either occur or become clinically meaningful. In that case, the MACS study may have failed to find any effect of heavy alcohol use on the progression of HIV disease simply because most of their sample were not truly heavy drinkers.

In studying the effects of chronic alcohol abuse on the course of HIV disease, important potential sources of bias must be considered. Chronic alcohol-abusing HIV+ individuals, as compared with light/nondrinking HIV+ individuals may: (1) seek treatment later in their disease, (2) have lower compliance with treatment regimens, (3) experience reduced treatment efficacy due to drug—alcohol interactions, (4) exhibit poor nutritional status, or (5) volunteer for studies at different intervals since HIV seroconversion. Because denial and avoidance are core phenomena associated with alcohol abuse, alcohol abusers may delay being tested for HIV, even if they have reason to believe they are infected. Furthermore, after testing HIV+, alcohol abusers may further delay seeking treatment. Samet,7 in a study of 118 HIV+ alcohol-abusing and nonalcohol-abusing subjects, documented a delay of ~1½ to 2 years between testing positive for HIV and seeking primary care treatment in the alcohol abusers, compared with a period of ~3 months in nonalcohol abusers. Moreover, alcohol abusers
As discussed earlier, the synergistic effects of alcohol and HIV on CNS morbidity have been shown to reduce the individual's response to illness. The individual who has had control of his drinking is less likely to reduce his alcohol consumption appropriately in illness by reducing his drinking to an extent that CNS suffers the additive effects of alcohol abuse and HIV disease. In conclusion, we have shown in a cross-sectional study using a longitudinal study design that participants with chronic hepatitis C and/or HIV disease who have moderate or heavy alcohol consumption are more likely to develop chronic mental health problems than those who have not. The synergistic effects of alcohol and HIV on CNS morbidity are not only seen in individuals with chronic hepatitis C and HIV disease but also in those without these diagnoses. The synergistic effects of alcohol and HIV on CNS morbidity may be related to the development of chronic mental health problems.
tic). If that is the case, the role of alcohol abuse treatment will become even more important in the management of HIV disease.

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