Fulminant encephalopathy with basal ganglia hyperintensities in HIV-infected drug users

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ABSTRACT

Objective: To define a clinical syndrome associated with active drug abuse in HIV-infected individuals.

Methods: We performed a retrospective review to identify individuals treated at the Johns Hopkins Hospital from 1993 to 2008 who were HIV-infected and were actively abusing drugs and had bilateral basal ganglia lesions on MRI. They were identified using a key word search in the radiology database, autopsy database, and the Moore HIV clinic database. Clinical, laboratory, and radiographic findings were correlated to define the syndrome.

Results: Ten individuals were identified who presented with a change in mental status or seizures, used cocaine or cocaine with heroin, had uncontrolled HIV infection ($>190,000$ copies/mL of plasma), elevated CSF protein (63–313 mg/dL), and diffuse hyperintense bilateral basal ganglia lesions on imaging. The majority of patients (8/10) had renal failure and despite supportive therapy most (7/9) ultimately died (median survival 21 days). Postmortem examination in one individual showed the presence of overwhelming microglial activation in the basal ganglia. The 2 surviving individuals were started on combined antiretroviral therapy (CART) during hospitalization.

Conclusion: We describe a unique clinical syndrome of a fulminant encephalopathy associated with primarily basal ganglia involvement in HIV-infected drug abusers. This syndrome is a rare but serious condition that is associated with a high mortality rate. Early CART institution may be useful and neuroprotective in this disorder, although this requires further investigation.

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GLOSSARY

CART = combined antiretroviral therapy; **FLAIR** = fluid-attenuated inversion recovery.

Many individuals with HIV infection abuse drugs, yet the neurologic complications of the combined effects of HIV infection and drug abuse are poorly understood. It is well known that drug abuse leads to noncompliance with antiretroviral therapy, resulting in HIV disease progression and increased mortality.¹ Cocaine and heroin use are more common in HIV-infected individuals than the general population and their use predicts poor HIV outcomes due to less virologic suppression and increased risk of opportunistic infections.² Active cocaine use is associated with less viral suppression than other illicit drugs including heroin.³ Cocaine and heroin are often used together as “speedball.” However, their combined effects on the brain have not been studied.

CNS complications often develop in HIV-infected patients and for unclear reasons the basal ganglia is a common site of involvement.⁴ Functional imaging and pathologic studies demonstrate the presence of basal ganglia abnormalities in HIV-infected individuals, which correlate with cognitive impairment.⁵ Additionally, active drug abuse in individuals with HIV infection may promote a synergistic effect on brain injury.⁶

Bilateral basal ganglia hyperintense lesions on MRI have rarely been seen in HIV-infected drug users, but are associated with increased mortality.^{7–9} We found several cases

Supplemental data at
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from our institution of HIV-infected cocaine and heroin users who developed a fulminant encephalopathy associated with primarily basal ganglia involvement on neuroimaging. The purpose of this study was to define the clinical manifestations and prognostic features of this syndrome and suggest guidelines for treatment.

METHODS **Standard protocol approvals, registrations, and patient consents.** This study was approved by The Johns Hopkins University Institutional Review Board (#NA_00004476).

Study procedures. We performed a retrospective review of HIV-infected active drug abusers treated at the Johns Hopkins Hospital from January 1993 to December 2008 with bilateral basal ganglia lesions. Individuals with an infectious or neoplastic cause for the basal ganglia lesions were excluded. Patients were identified using 3 separate databases: radiology, autopsy, and the Moore HIV clinic database. Key words searched included HIV, AIDS, encephalopathy, encephalitis, cocaine, drug abuse, basal ganglia lesions (unilateral or bilateral), and CD4 count <200 cells/mm³. Of 2,619 patients identified from the radiology database, 194 had basal ganglia lesions, of which 8 had bilateral lesions of noninfectious etiology. Of 103 patients identified from the Moore HIV clinic database and of 32 patients found in the autopsy database, 2 fulfilled our inclusion criteria. Four additional HIV-infected non-drug abusers were identified with bilat-

eral basal ganglia lesions due to HIV infection alone. These individuals were compared to the HIV-infected active drug abusers.

Autopsy results were available for one patient. Postmortem brain specimen was formalin-fixed, sectioned per standard protocol, and evaluated microscopically. The data collected were correlated to define a clinico-radiologic syndrome.

Immunocytochemical staining. Identification of astroglia, activated microglia, and HIV-p24 antigen was performed using specific primary antibodies on tissue sections by the avidin-biotin-peroxidase complex method according to established protocols.¹⁰ Multiple sections from the basal ganglia and frontal cortex were immunostained. Astrocytes were identified with anti-glial fibrillary acid protein antibodies (Dako, Temecula, CA, dilution 1:200), activated microglia with anti-IBA-1 (Wako, Inc., dilution 1:100), and anti-HIV p24 antibodies (Dako, Temecula, CA, dilution 1:50).

RESULTS **Case report.** A 50-year-old man with HIV infection (diagnosed in 1996), noncompliant with antiretroviral therapy, an active cocaine and heroin user, and with hepatitis C infection, was admitted in July 2008 after a partial seizure with secondary generalization. He had an altered mental status, but followed simple commands. The CD4 cell count was 17 cells/mm³ and HIV plasma viral load was 233,678 copies/mL. He had acute renal failure (creatinine 10.3 mg/dL) from obstructive uropathy.

Figure 1 Brain MRI of HIV-infected drug user

(A) Brain MRI of patient 5, (B) brain MRI of patient 7; both demonstrate diffuse bilateral basal ganglia hyperintensities and bilateral thalamic hyperintensities on T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) images. The lesions have no restriction on diffusion-weighted imaging (DWI) and their corresponding (apparent diffusion coefficient [ADC]) images are hyperintense.

Table 1 Patient characteristics and clinical details

Patient	Gender	Age, y	Presenting symptoms	Pertinent comorbidities	Reported drug use	Illness onset before admission, d	Duration of illness, d	Follow-up status
1	F	44	Seizure	ARF, HC	Cocaine, heroin	2	Unknown	Lost to f/u
2	M	33	AMS	ARF, HC	Cocaine	14	21	Died
3	M	45	Seizure	ARF, HC	Cocaine	2	133	Died
4	M	41	Seizure	CRF	Cocaine	0	19	Died
5	F	43	AMS	ARF, HC	Cocaine, heroin	1	65	Died
6	M	53	Seizure, AMS	HC	Cocaine	0	13	Alive ^a
7	M	50	Seizure, AMS	ARF, HC	Cocaine, heroin	1	19	Died
8	F	51	AMS, unsteady	None	Cocaine, heroin	3	193	Died
9	M	28	Seizure, AMS	ARF	Heroin	1	6	Alive ^a
10	M	41	Seizure	CRF	Cocaine, heroin	0	40	Died
Mean ± SD	—	43 ± 7.8	—	—	—	2.4 ± 4.2	56.6 ± 64.6	—

Abbreviations: AMS = altered mental status; ARF = acute renal failure; CRF = chronic renal failure; f/u = follow-up; HC = hepatitis C.

^a Antiretroviral therapy initiated during hospitalization.

thy and a positive urine screen for cocaine and heroin.

Over the next few days, he had 2 generalized seizures requiring therapy with phenytoin. A percutaneous nephrostomy tube resulted in improved renal function (creatinine 3.3 mg/dL). CSF was acellular but had progressive increase in protein (table e-1 on the *Neurology*[®] Web site at www.neurology.org). The HIV viral load in the CSF was 2,641 copies/mL. CSF bacterial/mycobacterial/fungal cultures, toxoplasma antibodies, venereal disease research laboratory, and cryptococcal antigen were negative. Epstein-Barr virus, JC virus, herpes simplex virus 1 and 2, cytomegalovirus, varicella zoster virus, and arboviruses were undetectable by PCR in the CSF. MRI of the brain demonstrated diffuse hyperintense signal abnormalities within bilateral lentiform nuclei, thalami, and external capsules on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (figure 1A). There was no restricted diffusion abnormality and magnetic resonance angiography was normal.

The patient continued to deteriorate neurologically despite supportive therapy and improving renal function. By hospital day 11, he was lethargic, not following commands, bradykinetic, and spastic with multifocal myoclonus. He subsequently developed Cheyne-Stokes respirations and died 19 days after his initial symptom onset. Autopsy was not performed.

Clinical characteristics. Ten patients fulfilled the clinical (HIV-infected active drug abusers) and MRI criteria (noninfectious bilateral basal ganglia lesions) out of 2,754 cases during our study time period (ta-

ble 1). There were 7 men and 3 women (mean age 42.9 years; range 28–53 years). The initial onset of symptoms was a seizure (70%), altered mental status (60%), or both (30%). Their symptoms were acute, with the onset of illness 2.4 ± 4.2 days (mean ± SD) before hospitalization. Active cocaine use was reported in 90% of individuals; 60% also used heroin. On admission, 8 individuals had renal dysfunction (6 acute, 2 chronic) and 6 had a history of hepatitis C (only one had active disease). The duration of illness ranged from 6 to 193 days and ultimately 8 died (80%), despite improving metabolic derangements and supportive care. Four patients with the longest duration of illness developed sepsis associated with a protracted hospital course. Another patient with severe neurologic deficits was lost to follow-up. Interestingly, the 2 patients who survived were the only patients started on combined antiretroviral therapy (CART) during their initial hospitalization. One of these survivors did not have renal dysfunction.

We identified another 4 HIV-infected non-drug users with bilateral basal ganglia lesions. These patients had a subacute but progressive HIV dementia. They did not have seizures, altered mental status, or renal dysfunction. Urine toxicology screen was negative in all of these individuals. At last follow-up, 2 of the 4 individuals had died, one from sepsis and the other from end-stage HIV disease.

Viral, immune, and imaging findings. As shown in table 2, all individuals were severely immunocompromised, with CD4 counts of 19 ± 21 cells/mm³ (range 1–68) and HIV plasma viral loads of

Table 2 Laboratory findings

Patient	CD4, cells/mm ³	Plasma HIV VL, RNA copies/mL	CSF WBC ^a	CSF RBC ^a	CSF glucose, mg/dL ^a	CSF protein, mg/dL ^a	Urine drug screen	Admission creatinine, mg/dL	MRI findings, hyperintense T2/FLAIR lesions
1	19	N/A	1	0	76	63	Cocaine, heroin	1.9	B/L BG, pons
2	1	N/A	4	4,290	84	310	Cocaine	7.0	B/L BG, B/L thalami
3	9	N/A	0	0	52	193	Negative	2.8	B/L BG
4	68	192,392	1/12	0/12	43/49	116/100	N/A, anuric	12.7	B/L BG, B/L thalami, pons, PVWM
5	34	225,026	3/1	1/0	45/40	129/149	Cocaine, heroin	1.7	B/L BG, PVWM
6	5	507,736	0/2	655/64	53/57	199/123	Cocaine, heroin	1.2	B/L BG, B/L thalami
7	17	233,678	0/0/1	3/2/8	52/64/69	195/574/838	Cocaine, heroin	10.3	B/L BG, B/L thalami, B/L EC
8	4	426,435	0	3	57	76	Cocaine, heroin	1.1	B/L BG, PVWM
9	1	693,000	2	0	56	101	Heroin	7.5	B/L BG
10	30	N/A	1	0	63	330	N/A, anuric	9.9	B/L BG, B/L thalami, pons, temporal lobes
Mean ± SD	19 ± 21	379,711 ± 198,527	2 ± 3	336 ± 1,107	57 ± 12	233 ± 213	—	5.6 ± 4.4	—

Abbreviations: B/L = bilateral; BG = basal ganglia; EC = external capsule; FLAIR = fluid-attenuated inversion recovery; N/A = not available; PVWM = periventricular white matter; RBC = red blood cells; VL = viral load; WBC = white blood cells.

^a Consecutive lumbar puncture (LP) results are presented as first LP/second LP/third LP.

379,711 ± 198,527 copies/mL (range 192,392–693,000). On admission, their creatinine ranged from 1.1 to 12.7 mg/dL. Interestingly, in all individuals the CSF had an albumino-cytologic dissociation (protein range 63–838 mg/dL; leukocyte range 0–12). Infectious etiologies were excluded in all individuals. All of them had an MRI of the brain during their hospitalization which demonstrated obvious diffuse hyperintense lesions in the basal ganglia on T2-weighted or FLAIR sequences (figure 1, A and B). Five patients also had thalamic involvement (50%) and 6 had lesions outside the deep gray matter structures (60%). None of the lesions enhanced after gadolinium administration and there was no evidence of ischemia on diffusion-weighted imaging. In contrast, in the HIV-infected non-drug abusers, basal ganglia lesions were patchy in appearance (figure 2).

Neuropathologic results. Neuropathologic assessment was obtained on one individual (patient 10). Immunocytochemical staining was performed to identify astroglia, activated microglia, and HIV-p24 antigen by using specific primary antibodies on tissue sections. Diffuse microglial activation was found within the basal ganglia with superimposed areas demonstrating perivascular microglial nodules (figure 3). There was a lack of HIV infection within the basal

ganglia and no multinucleated giant cells or microinfarcts were identified.

DISCUSSION Morphologic features of the basal ganglia by radiography are usually normal in individuals with HIV infection except for atrophy with HIV dementia and calcification with congenital HIV infection. In rare cases, basal ganglia hyperintensities on MRI of HIV-infected drug abusers with associated high mortality may occur.⁷⁻⁹ In the current series, we identified 10 HIV-infected cocaine and heroin users who developed a unique clinical syndrome. The initial presentation was of an acute encephalopathy often accompanied by seizures. Nearly all individuals were actively using cocaine and half were also using heroin. The HIV infection was poorly controlled and upon admission the majority had accompanying renal dysfunction. All individuals had an elevated CSF protein without accompanying pleocytosis and impressive diffuse bilateral basal ganglia lesions that were nonenhancing and best visualized on T2-weighted and FLAIR imaging. Despite supportive therapy, most of these individuals died due to their fulminant neurologic condition (median survival 21 days). The 2 surviving individuals were the only ones started on CART during hospitalization, which suggests a possible neuroprotective effect

Figure 2 Brain MRI of an HIV-infected non-drug user

The MRI demonstrates patchy bilateral basal ganglia hyperintensities and bilateral thalamic hyperintensities on T2-weighted (T2W) images.

of antiretroviral therapy. Autopsy was performed on one active drug user which showed overwhelming microglial activation in the basal ganglia.

The pathophysiology of CNS complications from the combined effects of HIV infection and active drug abuse is a field of active investigation. Experimental studies show that drugs of abuse may synergize with HIV proteins, resulting in acceleration of neuronal injury.¹¹ The basal ganglia is frequently involved⁴ with an increased HIV viral load.¹² However, despite a high viral load in plasma, we were unable to find HIV infection in the basal ganglia in the one patient who was autopsied. HIV proteins with neurotoxic properties can cross the blood–brain barrier¹³ and can also travel along neuronal pathways to the basal ganglia,¹⁴ hence active replication in the basal ganglia may not be necessary for these effects.

Neuropathologic studies in an opiate-abusing cohort showed severe changes in HIV-infected drug abusers.¹⁵ Nonetheless, clinical studies in the pre-highly active antiretroviral therapy era did not find any differences in neurocognitive function between HIV-infected and uninfected drug abusers.¹⁶ However, cases of HIV-infected cocaine and methamphetamine abusing patients with severe basal ganglia dysfunction may occur.¹⁷ This suggests that a subset of individuals may be vulnerable to developing neurologic complications due to the combined effects of HIV and drug abuse. In the present study, cocaine abuse was a common denominator in all patients. Some abused heroin as well. Both cocaine and opiates, including morphine, which is the active metabolite of heroin, are implicated in basal ganglia toxicity. Opiates are not intrinsically toxic.¹⁸ How-

Figure 3 Neuropathologic assessment of an active drug user

Immunocytochemical staining was performed on patient 10, which demonstrates (A) diffuse microglial activation and (B) perivascular microglial nodule within the basal ganglia. ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; T2W = T2-weighted.

ever, chronic, intermittent opiate exposure disrupts secondary messenger cascades and increases oxidative stress,¹⁹ which may enhance the vulnerability of neurons to HIV proteins such as Tat and gp120.²⁰ In transgenic mice that express the HIV-Tat protein, morphine exposure had profound effects in the basal ganglia.²¹ Similarly, autopsy studies confirm injury to dopaminergic neurons in cocaine users.²² Cocaine use is occasionally associated with persistent choreoathetosis, tics, and seizures.²³ Cocaine synergizes with both Tat and gp120 to cause increased neuronal dysfunction.¹¹

Another possible mechanism of cocaine–HIV interaction occurs at the blood–brain barrier. In vitro

studies show that HIV proteins can alter endothelial cell function²⁴ and disrupt the blood–brain barrier.²⁵ Autopsy studies show extravasation of serum proteins in brain tissue of patients with HIV encephalitis.²⁶ An in vitro study showed that cocaine can enhance monocyte migration across the blood–brain barrier by inducing gene expression for adhesion molecules and other proteins important in remodeling of endothelial cells.²⁷ Our patients had elevated CSF protein levels. All except 2 patients had >100 mg/dL, and none of them had a pleocytosis. This albuminocytologic dissociation is consistent with a breakdown of the blood–brain barrier.

Experimental evidence shows that drugs of abuse can enhance HIV replication. Of these drugs, opiates have been the best studied. In nonhuman primate models of HIV infection, chronic morphine administration markedly increases viral loads in plasma and CSF.²⁸ Interestingly, μ -opioid receptor activation can increase the expression of some of the chemokine receptors that serve as coreceptors for HIV in susceptible cells.²⁹ Opiates also activate HIV replication in latently infected macrophages,³⁰ which is the major cell type in the brain that is productively infected with HIV. In a nonprimate model, morphine was shown to cause the evolution of the retroviral *tat* gene in ways that lead to rapid disease progression.³¹ Similarly, cocaine can cause increased HIV replication in macrophages^{32,33} and astrocytes,³⁴ which are the reservoirs for HIV within the brain. Additionally, cocaine exacerbates HIV infection in dendritic cells.³⁵ In the current series, the viral load in the plasma was extremely high, with >10⁵ copies/mL in all patients in whom the viral load was available. Thus some of these mechanisms may be operational in these patients.

In our study, individuals had a high incidence of renal dysfunction, likely due to multifactorial causes. HIV infection can be associated with a nephropathy secondary to direct infection of the tubular and glomerular epithelial cells.³⁶ Also, cocaine may have both acute and chronic effects on the vasculature including the renal arteries.³⁷ It can cause renal artery vasoconstriction, accelerated renal arteriosclerosis, rhabdomyolysis-related renal dysfunction, and renal infarctions or thrombotic microangiopathy.³⁷ Possibly the renal dysfunction in most of our patients led to decreased clearance of cocaine/heroin, causing further neuronal injury. It is unlikely that renal dysfunction alone could cause the clinical syndrome, since basal ganglia lesions have not been described in patients with HIV nephropathy without drug abuse and not all patients had significant renal dysfunction. In our current database of over 2,000 individuals, we did not find a single patient with bilateral basal gan-

glia lesions and renal dysfunction without HIV infection. However, an ischemic lesion in the basal ganglia may occur in patients with end-stage renal disease and diabetic microvascular disease that resolves with conservative therapy.³⁸

Seven of 10 patients also had hepatitis C, a common comorbidity in drug-using patients. In one study, minor cognitive dysfunction was attributed to hepatitis C infection,³⁹ but another larger multicenter study failed to find any significant effect of this infection on neurocognitive dysfunction in HIV-infected patients.⁴⁰ Hence hepatitis C infection was unlikely to be a significant contributor to the clinical syndrome.

Limitations of our study include its retrospective nature and a small cohort, both of which limit definitive conclusions about whether CART is truly neuroprotective in this syndrome. We did not compare our HIV patient population to patients without HIV, which could help elucidate whether the grave prognosis seen in this study is also seen in non-HIV conditions with bilateral basal ganglia lesions. Finally, using key words to search databases can result in a selection bias and under-represent how often a disorder actually occurs.

We describe a unique clinical syndrome in HIV-infected cocaine and heroin users manifesting as a fulminant encephalopathy with primarily basal ganglia involvement. Despite the prominent basal ganglia involvement, these patients lacked obvious basal ganglia findings, likely due to the fulminant nature of this condition. Since this disorder has an associated high morbidity and mortality, recognizing this syndrome early is paramount. Early institution of CART may be useful and neuroprotective in this syndrome, as shown by the 2 individuals who survived and were the only ones started on CART during hospitalization. Multicenter clinical studies for early recognition of this syndrome and intervention and studies designed to understand disease pathogenesis as well as clinicopathologic correlation are critically needed.

DISCLOSURE

Dr. Newsome serves on a scientific board for and has received funding for travel from Biogen Idec and receives research support from the Sylvia Lawry Physician Fellowship of the National Multiple Sclerosis Society. E. Johnson reports no disclosures. Dr. Pardo receives research support from the Bart McLean Research Fund for Neuroimmunology Research, Project Restore, and the Guthy Jackson Charitable Foundation. Dr. McArthur serves on a scientific advisory board for CNS Bio Services; receives publishing royalties for *Current Therapy in Neurologic Disease, 7th Edition* (Mosby, 2006); is an author on patents re: Device for thermal stimulation of small neural fibers and Immunophilin ligand treatment of antiretroviral toxic neuropathy; and receives research support from Biogen Idec, Pfizer Inc., the NIH, the National Multiple Sclerosis Society, and the Foundation for Peripheral Neuropathy. Dr. Nath serves on scientific advisory boards for Biogen Idec and DioGenix, Inc.; serves as an Associate Editor

for the *Journal of Neurovirology*; may accrue revenue on patents re: Tat as an immunogen, Diosgenin for Treatment of Neurodegenerative Diseases, Role of Kv Channels in Neuroregeneration and Protection, Role of Lomimoid compounds as neuroprotective agents, and Tat ELISA; has served as a consultant for Nerveda Inc. and Elan Corporation; receives research support from the NIH; and has served as an expert advice in medico-legal cases.

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